



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> :  C07D 471/18, A61K 31/44, 31/445, 31/455 // (C07D 471/18, 221:00, 221:00, 221:00)		A1	(11) International Publication Number: <b>WO 98/18798</b>  (43) International Publication Date: 7 May 1998 (07.05.98)	
(21) International Application Number: PCT/IB97/01282  (22) International Filing Date: 15 October 1997 (15.10.97)  (30) Priority Data: 60/028,804 30 October 1996 (30.10.96) US			(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(71) Applicant (for all designated States except US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).  (72) Inventor; and  (75) Inventor/Applicant (for US only): O'NEILL, Brian, Thomas [US/US]; 18 Clapboard Hill Road, Old Saybrook, CT 06475 (US).  (74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).			Published With international search report.	
(54) Title: PYRIDONE-FUSED AZABICYCLIC- OR CYTISINE DERIVATIVES, THEIR PREPARATION AND THEIR USE IN ADDICTION THERAPY				
(57) Abstract				
<p>Pyridone-fused azabicyclic compounds of formula (I), and their pharmaceutically acceptable salts and prodrugs, wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are defined below, intermediates and methods for their preparation. Compositions and methods for using compounds of formula (I) in the treatment of neurological and mental disorders related to a decrease in cholinergic function such as nicotine addiction, Huntington's Chorea, tardive dyskinesia, hyperkinesia, mania, dyslexia, schizophrenia, analgesia, attention deficit disorder (ADD), multi-infarct dementia, age related cognitive decline, epilepsy, neurological and mental disorders related to a decrease in cholinergic function, senile dementia of the Alzheimer's type, Parkinson's disease, attention deficit hyperactivity disorder (ADHD), anxiety, obesity, Tourette's Syndrome and ulcerative colitis.</p>				

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon	KR	Republic of Korea	PL	Poland		
CN	China	KZ	Kazakhstan	PT	Portugal		
CU	Cuba	LC	Saint Lucia	RO	Romania		
CZ	Czech Republic	LI	Liechtenstein	RU	Russian Federation		
DE	Germany	LK	Sri Lanka	SD	Sudan		
DK	Denmark	LR	Liberia	SE	Sweden		
EE	Estonia			SG	Singapore		

PYRIDONE-FUSED AZABICYCLIC- OR CYTISINE DERIVATIVES, THEIR PREPARATION AND THEIR USE IN ADDICTION THERAPY

Background of the Invention

This invention relates to azabicyclic compounds. More particularly it relates to pyridone-fused azabicyclic compounds of the formula I below. Compounds of formula I are useful in the treatment of addictive disorders such as the use of tobacco or other nicotine containing products

10 and also for the treatment or prevention of withdrawal symptoms caused by cessation of chronic or long term use of tobacco products. These compounds are also useful in the treatment of Huntington's Chorea, tardive dyskinesia, hyperkinesia, mania, dyslexia, schizophrenia, analgesia, attention deficit disorder (ADD), multi-infarct dementia, age related cognitive decline, epilepsy, neurological and mental disorders related to a decrease in cholinergic function such as

15 Huntington's Chorea, tardive dyskinesia, hyperkinesia, mania, dyslexia, schizophrenia, analgesia, attention deficit disorder (ADD), multi-infarct dementia, age related cognitive decline, epilepsy, neurological and mental disorders related to a decrease in cholinergic function, senile dementia of the Alzheimer's type, Parkinson's disease, attention deficit hyperactivity disorder (ADHD), anxiety, obesity, Tourette's Syndrome and ulcerative colitis.

20 The compounds of this invention may also be used in combination with a anti-depressants such as imipramine in order to treat both the cognitive decline and depression associated with AD; in combination with serotonin uptake inhibitors such as Zoloft to treat both the cognitive decline and depression associated with AD; in combination with muscarinic agonists in order to stimulate both central muscarinic and nicotinic receptors; in combination with neurotrophic factors such as

25 NGF in order to maximize cholinergic enhancement; in combination with agents which slow or arrest AD such as amyloid or tau inhibitors.

Substances which can deliver pharmacologically relevant amounts of nicotine to the central nervous system are among the most abused substances known. These include, but not are not limited to tobacco cigarettes, and "chewing tobacco" (see J. E. Henningfield, Ph.D, New

30 England Journal of Med., 1196, 1995). Cigarette smoking has been tied to increased risk for lung cancer, emphysema and heart disease and it is estimated 400,000 people will die in 1995 from the combined effects of nicotine abuse in the United States (see J. A. Califano, Jr., New England Journal of Med. 1214, 1995). Nicotine is a highly addicting drug with 40% of those who try smoking later becoming physically dependent upon it. Attempts to quit the use of nicotine, such as

35 in smoking, have been largely ineffective with > 80 % of such attempts ending in failure. Most attempts to quit end in failure in the first week due to intense withdrawal and craving symptoms. An effective therapy should aid in the cessation or lessening of tobacco use, prevent withdrawal,etc prevent withdrawal symptoms, relieve craving and, simultaneously, antagonize the reinforcing effects of nicotine obtained through smoking. Currently, few therapies are available for

40 smoking cessation and most involve replacement of cigarettes with nicotine in the form of a patch

5 or gum. A high rate of relapse and low overall success in ending nicotine use is evidence of the need for additional and more effective therapies for treatment of nicotine addiction than the nicotine patch or gum.

10 Pharmaceutical compositions employed for the treatment of chronic nicotinism and addiction to nicotine can be divided into two groups. The first covers salts of silver, iron and copper. These substances are employed to develop a negative reflex to smoking usually in the form of a solution, or by incorporation in chewing gum compositions. The resultant reflex is based on the appearance of a strong unpleasant taste in the mouth during smoking after a preliminary rinsing of the mouth cavity with solutions of salts, or after the use of a chewing gum containing such salts (See Nasirov *et al.* "Anabasine Hydrochloride - New Antismoking Agent", Chemico-Pharmaceutical Journal, vol. XII, 1978, No. 2, 149-152).

15 The second group of agents that are used for the suppression of nicotine addition comprises substances of an alkaloidal nature, such as 1,2,3,4,5,6-hexahydro-1,5-methanopyrido[1,2-a][1,5]diazocin-8-one (hereafter 'cytisine'), lobeline and anabasine hydrochloride, possessing an effect on H-cholinoreactive systems of the organism similar to that of nicotine. The 20 mechanism of their effect is due to their structural similarity with nicotine and the possible "competitive" antagonism between these alkaloids and nicotine (F.R. Khalikova, S.H. Nasirov, "On pharmacology of the Alkaloid Anabasine and some Polymeric and Copolymeric Derivatives Thereof", in Coll. "Pharmacology of Vegetable Compounds", Proceedings of Tashkent University, 457, 1973, 5-16).

25 United States Patent Number 4,971,079 describes a composition comprising a biologically resorbable polymer containing a cation exchange group modified by an antinicotine action alkaloid, such as anabasine or cytisine, and a gum containing same. However, it has been found that the potency of cytisine is not high due to its inability to penetrate the brain barrier. (Reavill, C. et al., Behavioural and Pharmacokinetic Studies On Nivotine, Cytisine and Lobeline, Neuropharmacology, 29, 619-624 (1990)). Labadie L.C. (Peut-on supprimer les facteurs de risque en bronchopatie chronique et en particulier le tabac", Mediator. med., 1976, 4, No. 112, 97, 99) describes the use of leaves of other night-shade plants, such as potato, tomato, eggplant and digitalis as tobacco substitutes.

30 One of the most successful approaches to date in reducing the incidence of smoking 35 relies upon nicotine containing chewing gum which is designed to reduce smoking withdrawal symptoms. The reported success rate, while still relatively low, is approximately twice that of the other methods which have heretofore been employed. (See British Medical Journal, 286, (1983)).

35 The use of the nicotine gum suffers from several problems including bad taste, destruction 40 of dental appliances and gastrointestinal discomfort thereby reducing their use to suppress nicotine addiction. In addition, it has been found that the nicotine containing gum does not

5 completely satisfy the craving that most smokers experience for nicotine and often nicotine gum becomes addictive to the patient.

A simulated smoking device which uses a source of vaporizable nicotine is claimed in U.S. Pat. No. 4, 284,089. While the cigarette itself is non-combustible it delivers a nicotine-containing vapor which may not raise the nicotine level in the blood sufficiently to satisfy a smoker.

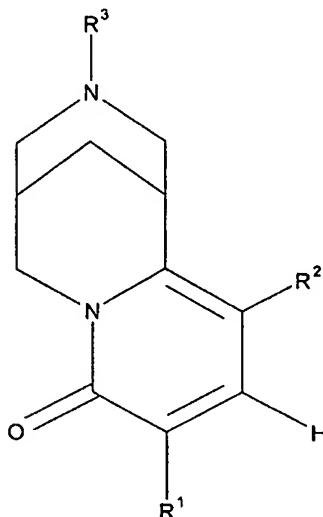
10 Thus, it has not been shown to satisfy the desire for a certain nicotine level in the blood to which many smokers have become accustomed and, even more so, upon which many smokers have become dependent. In addition, the simulated smoking devices of the type taught in U.S. Pat. No. 4,284,089 also suffer from the bad taste of a substantial amount of nicotine introduced into the oral cavity. More importantly, this nicotine does not penetrate into the chest for stimulating and 15 providing that sensation normally provided by nicotine and to which the smoker has become accustomed.

The current first line therapy for smoking cessation, as described in United States Patent Number 5,016,652 describes a transdermal patch which is useful for the controlled delivery of nicotine to the bloodstream of the user thereby reducing the incidence of smoking. Clinical trials 20 have shown that abstinence rates (with the nicotine patch) of 30 to 40% can be achieved during the first six weeks of application (K.J. Palmer, M.M. Buckley, D. Faulds; Drugs 44(3) 498-529, (1992) compared with 4 to 21% with a placebo. However, long term abstinence rates (>6 months) are considerably lower; falling to between 11-18%. Thus, a more effective therapy which will afford a greater percentage of smokers who are able to quit is clearly needed.

5

Summary of the Invention

This invention relates to pyridone-fused azabicyclic compounds of the formula



its enantiomers, diastereomers and stereoisomers, and their pharmaceutically acceptable salts and prodrugs,

10       wherein R<sup>1</sup> and R<sup>2</sup> are each independently selected from

- a)       H, halo, CF<sub>3</sub>, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, CH<sub>2</sub>OH, -C(O)R wherein R = H, (C<sub>1</sub> - C<sub>6</sub>) alkyl, aryl and benzyl including substituted alkyl, aryl and benzyl, C≡N, C≡CR, wherein R = H, (C<sub>1</sub> - C<sub>6</sub>) alkyl, aryl including substituted alkyl, aryl, -S(O)<sub>n</sub> R, wherein R = H, (C<sub>1</sub> - C<sub>6</sub>) alkyl, aryl including substituted alkyl, aryl and n = 0,1,2, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkenyl, H<sub>2</sub>N, di-[(C<sub>1</sub>-C<sub>6</sub>)alkyl]amino, (C<sub>1</sub>-C<sub>6</sub>)monoalkylamino, (C<sub>6</sub>-C<sub>10</sub>)aryl amino, (C<sub>3</sub>-C<sub>8</sub>)cycloalkylamino, heteroaryl amino, cycloheteroalkylamino and CON(R<sup>5</sup>)<sub>2</sub> wherein each R<sup>5</sup> is selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl and (C<sub>6</sub>-C<sub>10</sub>)aryl; and
- b)       CO<sub>2</sub>R wherein R is selected from H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, phenyl and benzyl; and
- c)       optionally benzene-fused (C<sub>6</sub>-C<sub>10</sub>)aryl, optionally benzene-fused (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, optionally benzene-fused heteroaryl and optionally benzene-fused cycloheteroalkyl, wherein said heteroaryl group contains five to ten atoms comprising one to four heteroatoms, said cycloheteroalkyl contains 4 to 8 atoms comprising one or two heteroatoms selected from N, S and O;

25       and wherein any of the alkyl, alkenyl, aryl, cycloalkyl, cycloheteroalkyl and heteroaryl groups in a), b) and c) are optionally substituted with one or more substituents selected from halogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, hydroxy, hydroxymethyl, CHO and CO<sub>2</sub>R wherein R is as described above; and

R<sup>3</sup> is selected from H, optionally substituted benzyl and methyl;

5 with the provisos that R<sup>1</sup> and R<sup>2</sup> are not both hydrogen and when R<sup>3</sup> is H, then R<sup>1</sup> and R<sup>2</sup> when selected from H, Br and Cl, cannot be the same.

In the above compounds, "aryl" includes, without limitation, optionally substituted phenyl and naphthyl, "cycloalkyl" includes, without limitation, optionally substituted cyclopentyl and cyclohexyl, and said cycloalkyl group may also be unsaturated, and "heteroaryl" includes, without limitation, thienyl, furyl, pyrano, pyrrolo, imidazolyl, oxazolyl, thiazolyl, tetrazolyl, triazolyl, pyrazinyl and pyridyl, and said "cycloheteroalkyl" includes, without limitation, pyrrolidinyl, piperidinyl, tetrahydrofuryl and tetrahydropyrano.

Preferred compounds of formula I are those wherein R<sup>3</sup> is selected from H, benzyl or methyl and R<sup>1</sup> and R<sup>2</sup> are each independently selected from H, halo, (C<sub>1</sub>-C<sub>6</sub>)alkyl, cyano, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>1</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl-R and -C(O)R wherein R is H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>5</sub>-C<sub>10</sub>)aryl and (C<sub>5</sub>-C<sub>9</sub>)heteroaryl and amino and mono and di-substituted amino; with the provisos that when R<sup>3</sup> is H then R<sup>1</sup> and R<sup>2</sup> are not both H, Br and Cl and when R<sup>3</sup> is benzyl or methyl then R<sup>1</sup> and R<sup>2</sup> are not hydrogen.

More preferred compounds of formula I are those wherein R<sup>1</sup> and R<sup>2</sup> are each independently selected from H, ethyl, methyl, phenyl, vinyl, fluoro, bromo, chloro, isopropyl, tert-butyl, trifluoromethyl, acetyl, propanoyl, 2,2-dimethylpropanoyl, 2-methylpropanoyl, butanoyl, pentanoyl, cyano, di-[(C<sub>1</sub>-C<sub>6</sub>)alkyl]amino, (C<sub>1</sub>-C<sub>6</sub>)monoalkylamino, (C<sub>6</sub>-C<sub>10</sub>)arylamino, (C<sub>3</sub>-C<sub>8</sub>)cycloalkylamino, heteroarylamino, cycloheteroalkyamino and CON(R<sup>5</sup>)<sub>2</sub> wherein each R<sup>5</sup> is selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl and (C<sub>6</sub>-C<sub>10</sub>)aryl; (C<sub>6</sub>-C<sub>10</sub>)aryl and (C<sub>5</sub>-C<sub>9</sub>)heteroaryl wherein the aryl and heteroaryl groups are optionally substituted with one or more substituents selected from halogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, hydroxy, hydroxymethyl, CHO and CO<sub>2</sub>R.

More preferred compounds of formula I are those wherein R<sup>3</sup> is selected from optionally substituted benzyl or (C<sub>1</sub>-C<sub>6</sub>)alkyl, wherein the substituents are described above and R<sup>1</sup> and R<sup>2</sup> are each independently selected from hydrogen, halo, cyano, optionally substituted (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkenyl, amino, di-[(C<sub>1</sub>-C<sub>6</sub>)alkyl]amino, (C<sub>1</sub>-C<sub>6</sub>)monoalkylamino, (C<sub>6</sub>-C<sub>10</sub>)arylamino, (C<sub>3</sub>-C<sub>8</sub>)cycloalkylamino, heteroarylamino, cycloheteroalkyamino and CON(R<sup>5</sup>)<sub>2</sub> wherein each R<sup>5</sup> is selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl and (C<sub>6</sub>-C<sub>10</sub>)aryl; -C(O)R wherein R is H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>5</sub>-C<sub>10</sub>)aryl and (C<sub>5</sub>-C<sub>9</sub>)heteroaryl; (C<sub>6</sub>-C<sub>10</sub>)aryl or (C<sub>5</sub>-C<sub>9</sub>)heteroaryl wherein the substituents are described above.

35 More particularly, the invention relates to compounds of the formula I wherein R<sup>1</sup> and R<sup>2</sup> are each independently selected from hydrogen isopropyl, tert-butyl, trifluoromethyl, acetyl, propanoyl, 2,2-dimethylpropanoyl, 2-methylpropanoyl, butanoyl, pentanoyl, cyano, 2,4-difluorophenyl, 2-fluorophenyl, 2- and 3-thienyl, dimethylamino and R<sup>3</sup> is selected from hydrogen, benzyl, methyl and R<sup>1</sup> and R<sup>2</sup> are each independently selected from hydrogen, bromo, chloro, ethyl, methyl, fluoro, vinyl and phenyl.

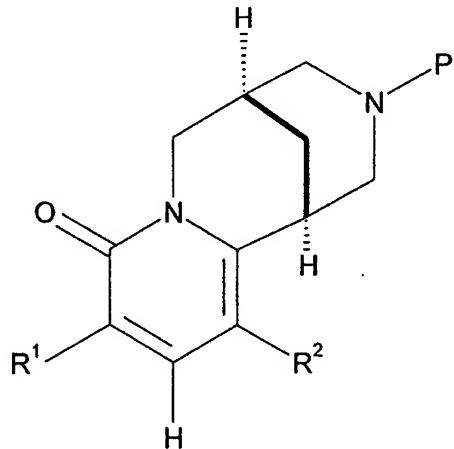
5        Most preferred compounds of the formula I are selected from:  
9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
10      9-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9,11-difluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
15      9,11-diethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9,11-dimethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
20      11-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9,11-diphenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9,11-divinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
25      9-bromo-3-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
3-benzyl-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
and  
3-benzyl-9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one.  
Most preferred compounds of the formula I are selected from:  
30      9-morpholino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-benzylamino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-pyrrolidino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-dimethylamino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
35      9-(2-tetrahydrofuryl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-  
one  
9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-ethynyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

5        9-(2-propenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-propyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-methoxyphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
10      9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-[2-(1,1,1-trifluoromethylpropenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a]  
[1,5]diazocin-8-one;  
9-(4-methoxyphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-ethoxy-5-methylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a]  
15      [1,5]diazocin-8-one;  
9-(2-benzofuranyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-thienyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(3-thienyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-[3-(4-methylthienyl)]-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-  
20      one;  
9-[2-(3-methylthienyl)]-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-  
one;  
9-[3-(2-fluoropyridyl)]-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-pyridyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
25      9-(2-furanyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(3-furanyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-trifluoromethylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a] [1,5]diazocin-  
8-one;  
9-(4-trifluoromethylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a] [1,5]diazocin-  
30      8-one;  
9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
11-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-methylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(3-acetylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
35      9-(2-chlorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(3,4-dichlorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-  
one;  
9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(4-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

5        9-(3-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
       9-(3,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
       9-(2,4-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
       9-(2-fluoro-4-chlorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

10      9-(2-fluoro-4-methoxyphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
       9-(2,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
       9-(2-thiazoyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one.

The invention also relates to compounds of the formula



15      III  
       wherein P is defined as R³ or is selected from t-butoxycarbonyl (t-BOC), acetyl, benzoyl, trifluoroacetyl and carbobenzyloxy (CBZ) and R¹ and R² are each independently selected from H, halo, boronic acid, carboalkoxy, carboxyaldehyde, cyano, ethynyl, acyl, 2-propenyl, amino, mono and dialkylamino, aryl and heteroaryl with the proviso that R¹ and R² are not both hydrogen.

Preferred compounds of the formula III, as described above, are those wherein P is t-BOC, acetyl and trifluoroacetyl and each R¹ and R² is independently selected from hydrogen, fluoro, bromo, chloro, iodo, (C<sub>1</sub>-C<sub>6</sub>)alkyl, carboalkoxy, carboxyaldehyde, cyano, acetyl, propanoyl, 2,2-dimethylpropanoyl, 2-methylpropanoyl, butanoyl, pentanoyl, 2-propenyl, dimethylamino, with the proviso that R¹ and R² are not both hydrogen.

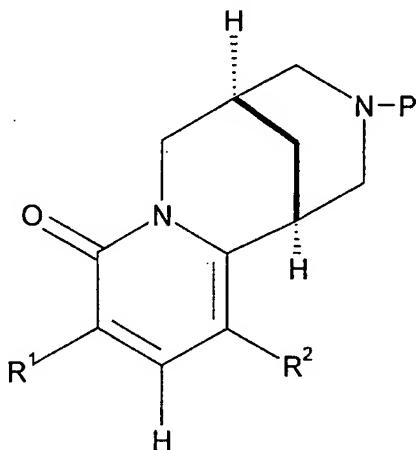
Most preferred compounds of formula III are selected from:

5            N-t-BOC-9-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
N-t-BOC-9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
N-cBz-9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
N-trifluoroacetyl-9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-  
one;  
10          N-trifluoroacetyl-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-  
one;  
N-acetyl-9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
N-tBOC-9-boronic acid -1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-  
one;  
15          N-acetyl-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
N-t-BOC-9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
N-trifluoroacetyl-9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-  
one;  
N-cBz-9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
20          N-acetyl-9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
N-t-BOC-9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
N-t-BOC-9-ethynyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
N-t-BOC-9-dimethylamino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-  
one;  
25          N-t-BOC-9-(2-propenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-  
one;  
N-t-BOC-9-(2-propyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
N-t-BOC-9-(2-(1,2-propanediol)-1,2,3,4,5,6-hexahydro-1,5-methano-  
pyrido[1,2a][1,5]diazocin-8-one;  
30          N-t-BOC-9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-  
one;  
N-t-BOC-9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-  
one;  
N-t-BOC-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
35          N-t-BOC-11-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
N-t-BOC-9,11-dibromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-  
one (9,11-dibromo-t-BOC-cytisine);  
N-t-BOC-9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
N-t-BOC-11-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;

-10-

5 N-t-BOC-9,11-dichloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
 N-t-BOC-9-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
 N-t-BOC-11-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
 and  
 10 N-t-BOC-9,11-difluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one.

The invention also relates to compounds of the formula



II

wherein R<sup>4</sup> is H, P is selected from t-butoxycarbonyl (t-BOC), acetyl, benzoyl, trifluoroacetyl  
 15 and carbobenzyloxy (CBZ), and R<sup>1</sup> and R<sup>2</sup> are each independently selected from H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkenyl and (C<sub>6</sub>-C<sub>10</sub>)aryl, with the proviso that R<sup>1</sup> and R<sup>2</sup> are not both hydrogen.

More particularly, the invention provides compounds of formula II, as described above, wherein R<sup>1</sup> and R<sup>2</sup> are each independently selected from H, ethyl, methyl, vinyl and phenyl.

Most preferred compounds of formula II are selected from

20 N-t-BOC-11-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one  
 (11-vinyl-t-BOC-cytisine);  
 N-t-BOC-11-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one  
 (11-ethyl-t-BOC-cytisine); and  
 N-t-BOC-11-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one  
 25 (11-phenyl-t-BOC-cytisine).

5 Unless otherwise indicated, the term "halo", as used herein, includes fluoro, chloro, bromo and iodo.

Unless otherwise indicated, the term "alkyl", as used herein, may be straight, branched or cyclic, and may include straight and cyclic moieties as well as branched and cyclic moieties.

10 Unless otherwise indicated, the term "one or more substituents", as used herein, refers to from one to the maximum number of substituents possible based on the number of available bonding sites.

15 The term "one or more carbons of said non-aromatic ring", as used herein, refers to from one to all of the carbon atoms that are part of the non-aromatic ring of any of the aryl-fused or heteroaryl-fused systems described above, and not part of the aromatic ring of said aryl-fused system.

The term "one or more carbons of said aromatic ring", as used herein, refers to from one to all of the carbon atoms that are part of the aromatic ring of any of the aryl-fused and heteroaryl-fused systems described above.

20 The compounds of formula I have optical centers and therefore may occur in different enantiomeric configurations. The invention includes all enantiomers, diastereomers, and other stereoisomers of such compounds of formula I, as well as mixtures thereof.

25 The present invention also relates to all radiolabelled forms of the compounds of the formulae I. Preferred radiolabelled compounds of formula I are those wherein the radiolabels are selected from as <sup>3</sup>H, <sup>11</sup>C, <sup>14</sup>C, <sup>18</sup>F, <sup>123</sup>I and <sup>125</sup>I. Such radiolabelled compounds are useful as research and diagnostic tools in metabolism pharmacokinetics studies and in binding assays in both animals and man.

30 The present invention also relates to a pharmaceutical composition for use in reducing nicotine addiction or to aid in the cessation or lessening of tobacco use in a mammal comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt or prodrug thereof, effective in reducing nicotine addiction or to aid in the cessation or lessening of tobacco use and a pharmaceutically acceptable carrier.

35 The present invention also relates to a method for reducing nicotine addiction in a mammal, comprising administering to a mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt or prodrug thereof, effective in reducing nicotine addiction or lessening of tobacco use.

Examples of pharmaceutically acceptable acid addition salts of the compounds of formula I are the salts of hydrochloric acid, p-toluenesulfonic acid, fumaric acid, citric acid, succinic acid, salicylic acid, oxalic acid, hydrobromic acid, phosphoric acid, methanesulfonic acid, tartaric acid, maleate, di-p-toluoyl tartaric acid, and mandelic acid.

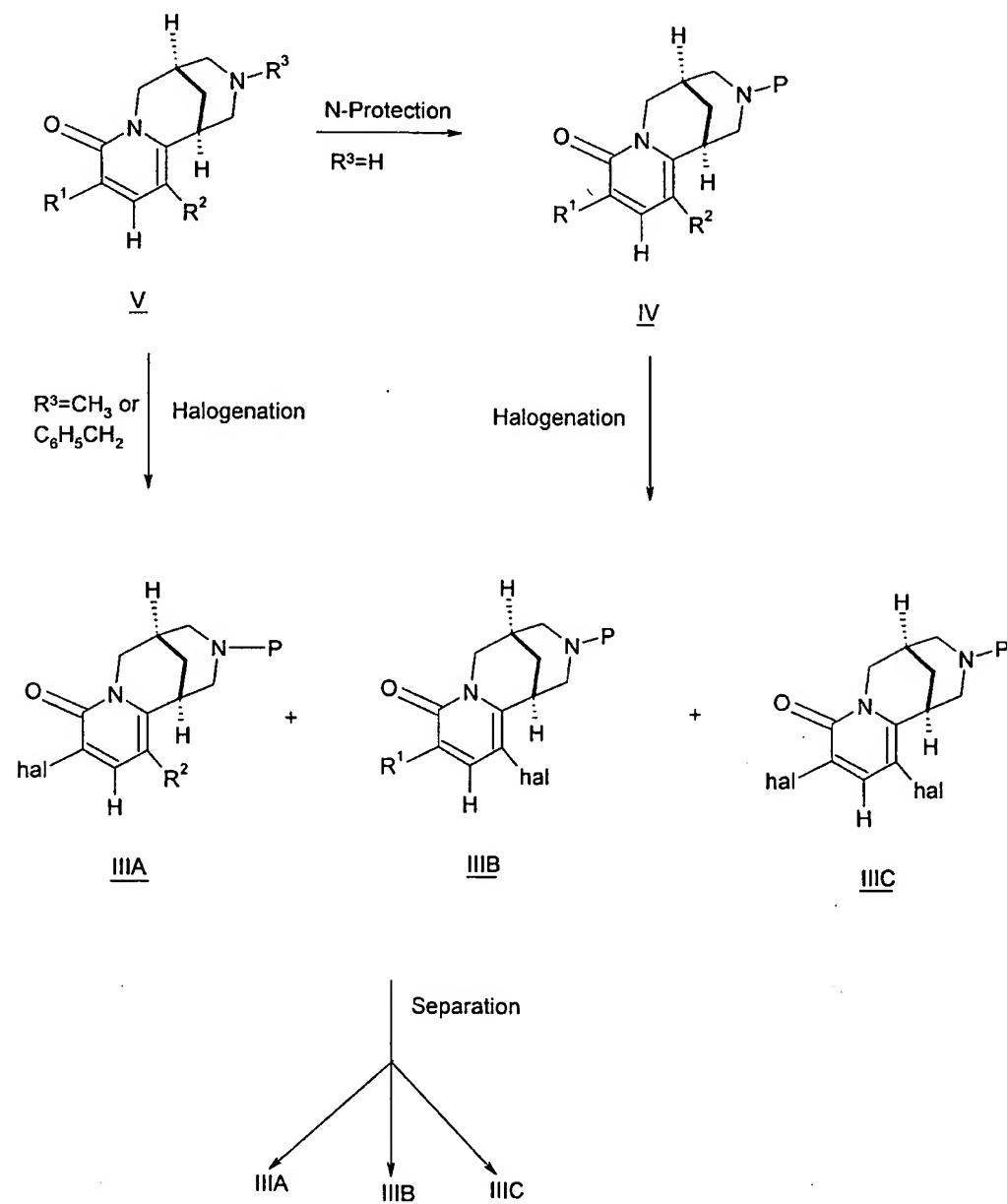
-12-

5

Detailed Description of the Invention

Except where otherwise stated, R, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup>, and formulae I, II, III, IV and V, in the reaction schemes and discussion that follow are defined as above.

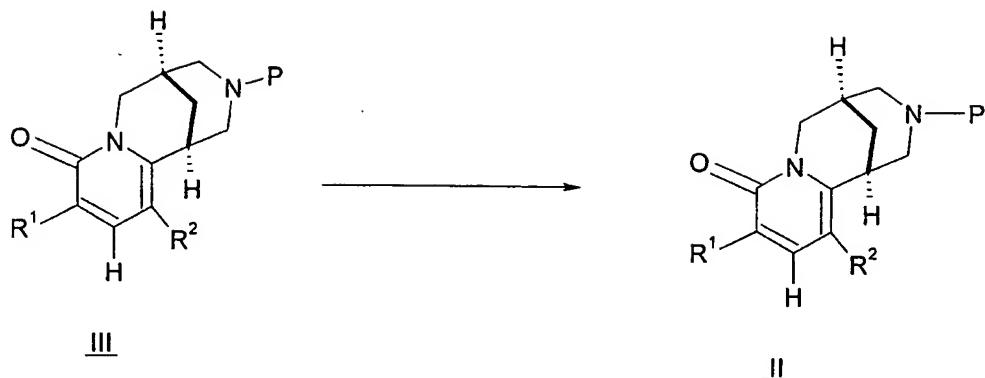
SCHEME 1



-13-

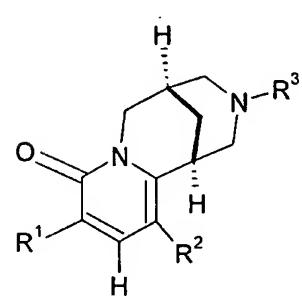
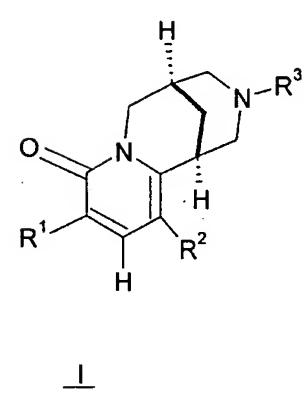
5

## SCHEME 2



A.  $R^1=\text{halo}$ ,  $R^2=R^4=\text{H}$   
 B.  $R^2=\text{halo}$ ,  $R^2=\text{H}$   
 C.  $R^1=R^2=\text{halo}$ ,  $R^4=\text{H}$

A.  $R^1=\text{alkyl, alkenyl or phenyl}$ ,  $R^2=\text{H}$   
 B.  $R^2=\text{alkyl, alkenyl or phenyl}$ ,  $R^1=\text{H}$   
 C.  $R^1=R^2=\text{alkyl, alkenyl or phenyl}$



A.  $R^1=\text{halo}$ ,  $R^2=R^3=\text{H}$   
 B.  $R^2=\text{halo}$ ,  $R^1=R^3=\text{H}$   
 C.  $R^1=R^2=\text{halo}$ ,  $R^3=\text{H}$

A.  $R^1=\text{alkyl, alkenyl or phenyl}$ ,  $R^2=R^3=\text{H}$   
 B.  $R^2=\text{alkyl, alkenyl or phenyl}$ ,  $R^1=R^3=\text{H}$   
 C.  $R^1=R^2=\text{alkyl, alkenyl or phenyl}$ ,  $R^3=\text{H}$

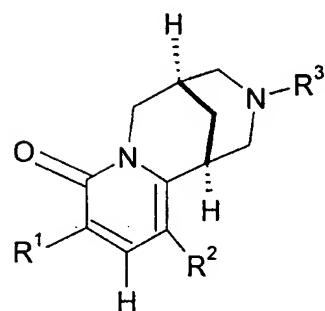
-14-

5

## SCHEME 3

V or I ( $R^3=H$ )

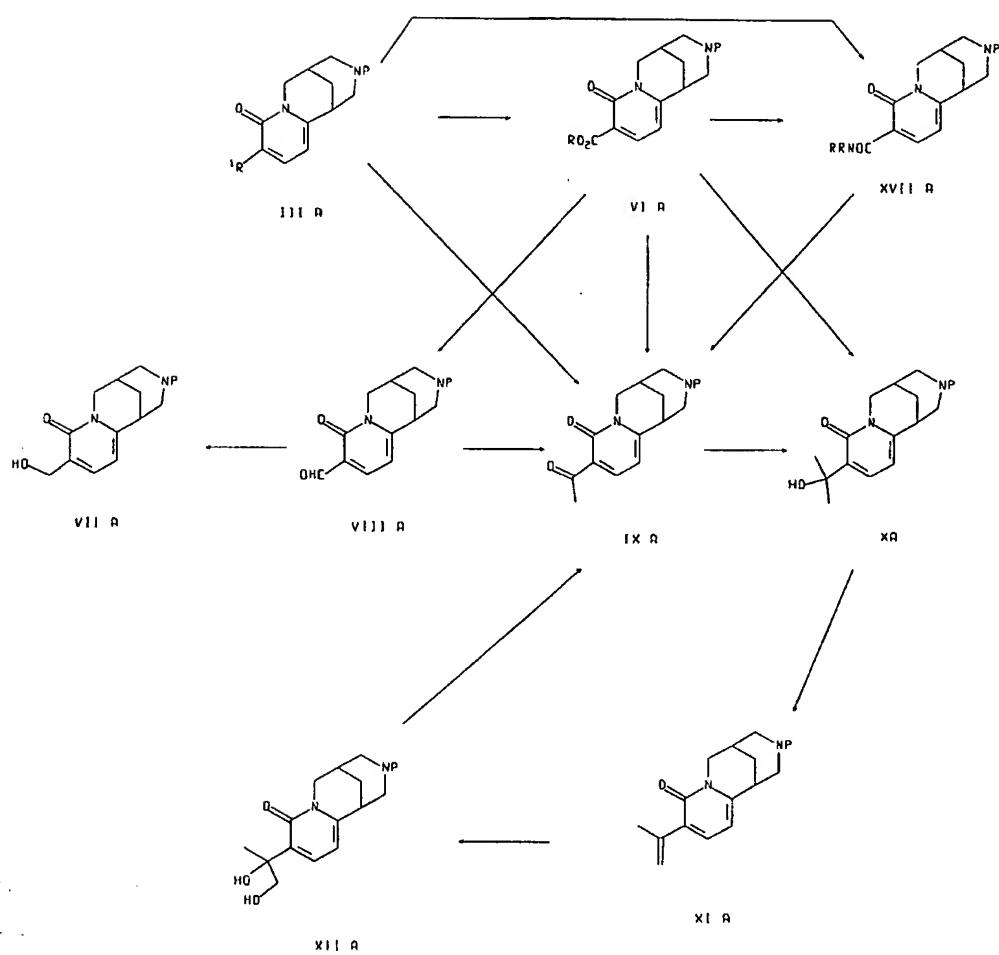
Alkylation



I

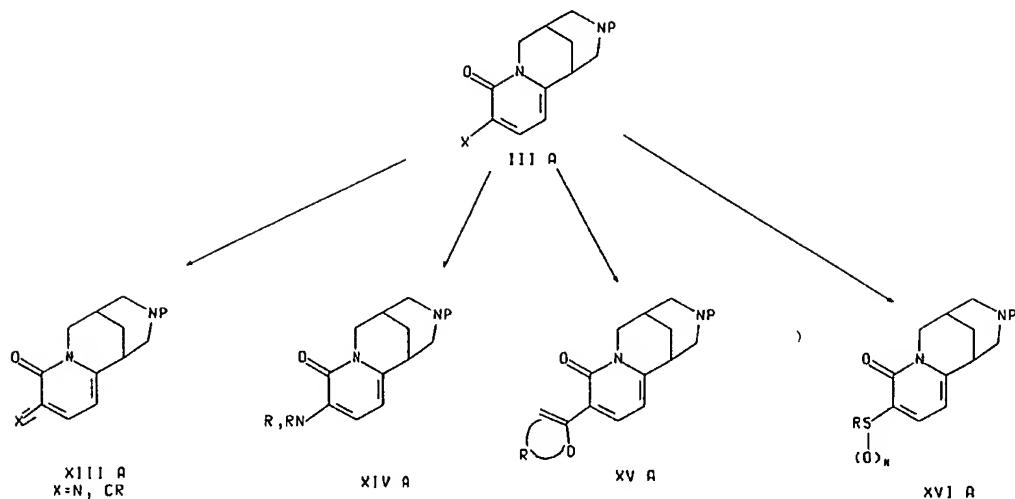
( $R^3=$ benzyl or methyl and  
 $R^1$  and  $R^2$  are as defined above  
for V or I)

#### SCHEME 4



5

## SCHEME 5



5        In each of the reactions discussed below, or illustrated in Schemes 1-3, above, pressure is not critical unless otherwise indicated. Pressures from about 0.5 atmospheres to about 5 atmospheres are generally acceptable, with ambient pressure, i.e., about 1 atmosphere, being preferred as a matter of convenience.

Referring to Scheme 1, compound **V** (cytisine, when R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are all hydrogen) is  
10      protected to form the compound of the formula **IV** wherein **P** is an appropriate nitrogen protecting group, as known in the art, including t-BOC, CBZ, methyl, benzyl, trifluoroacetyl, acetyl and benzoyl. If desired, the N-protection step may be eliminated. Compound **IV** (or **V** wherein R<sup>3</sup> is methyl or benzyl) is halogenated to form a mixture of halogenated products of the formula **III** wherein one or both of R<sup>1</sup> and R<sup>2</sup> is a halogen atom, depending upon the conditions and the  
15      reaction stoichiometry, preferably iodo, bromo or chloro. Thus, when using one molar equivalent of a suitable halogenating agent, products **IIIA** and **IIIB** predominate. However, when two molar equivalents of halogenating agent are used compound **IIIC** predominates. The nitrogen can be protected by acetyl and trifluoroacetyl, t-BOC, CBZ, benzyl, methyl or any of the readily removable N-protecting groups known in the art. Alternatively, no protecting group need be used.

20      The t-BOC group can be introduced using a reagent such as di-t-butyldicarbonate, di-t-butylpyrocarbonate, 2-(t-butoxycarbonyloxyimino)-2-phenylacetonitrile (t-BOC-ON), t-BOC-azide, t-BOC-chloride, t-BOC-fluoride and 2-(t-butoxycarbonyloxy)phthalimide or similar reagents wherein t-BOC refers to the residue tertiary butoxycarbonyl a useful protecting group. The reaction is conducted in a suitable solvent or mixture of solvents, including, but not limited to the following:  
25      methylene chloride, ethyl acetate, chloroform, benzene, toluene, ether, tetrahydrofuran (THF), dichloroethane and water with a suitable base including, but not limited to, the following: sodium, lithium and potassium carbonates, bicarbonates and hydroxides, imidazole, dimethylaminopyridine and trialkylamines such as triethylamine. The reaction requires 0.5 to 24 hours for completion. The temperature is not critical, the reaction being run between room  
30      temperature and the reflux temperature of the solvent or mixture of solvents. The reaction is generally run at a pressure between 0.5 and 2.0 atmospheres, preferably at atmospheric pressure. It is preferably carried out at reflux for 1 - 2 hours with t-BOC dicarbonate in a mixture of methylene chloride and water with sodium bicarbonate as base. If the protecting group is CBZ (carbobenzyloxy) it can be incorporated by the general procedure described above beginning with  
35      the compound of the formula **V** and carbobenzyloxy chloride (CBZ - Cl) instead of the t-BOC source.

Referring to Scheme 3, the N-methyl or N-benzyl group can be introduced by nitrogen alkylation of cytisine or the compound of the formula **I** (or **V** when R<sup>3</sup> is hydrogen) with a suitable reagent. Suitable reagents for N-benzylation include benzyl halides, such as the bromide, chloride and iodide and sulfonic acid esters such as the mesylate, tosylate and triflate in an inert solvent  
40

5 such as dimethylformamide (DMF), N-methylpyrrolidone, dimethylsulfoxide (DMSO), acetone, ethanol, methanol, acetonitrile, THF and water and mixtures thereof with a base such as sodium or potassium hydride, 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU), potassium t-butoxide, tri(C<sub>1</sub>-C<sub>6</sub>)alkylamines such as triethylamine, sodium, lithium and potassium carbonates, bicarbonates and hydroxides, imidazole and dimethylaminopyridine. Aprotic solvents must be used when the  
10 bases, such as the hydrides, are reactive to protic solvents such as water. The reaction can be run at temperatures between 0°C and the reflux temperature of the solvent for a period of 0.5 hours to 48 hours. It is preferably carried out with benzyl chloride in acetone at reflux for 1 - 2 hours using potassium carbonate as base at atmospheric pressure.

15 For N-methylation, suitable reagents are methyl iodide or bromide, dimethylsulfate and methyl triflate using the conditions described above for N-benzylation. The reaction is preferably carried out with methyl iodide in acetone at reflux for 1 -2 hours using potassium carbonate as base.

20 Alternatively, N-benzylation may be carried out in the following manner. The compound of formula I (or V wherein R<sup>3</sup> is hydrogen), in an inert solvent, such as (C<sub>1</sub>-C<sub>6</sub>)alkanols, preferably methanol or ethanol, and halocarbons such as methylene chloride, chloroform and dichloroethane and acetic acid and water and mixtures thereof, is treated with benzaldehyde and a reducing agent such as sodium triacetoxyborohydride, tetraalkylammonium triacetoxyborohydride, sodium cyanoborohydride, sodium borohydride or similar reagents with or without a catalytic amount of an acid, such as acetic acid or trifluoroacetic acid at a temperature between 0°C and the reflux  
25 temperature of the solvent, or mixture of solvents, for a period of 0.5 to 48 hours at atmospheric pressure. The reaction is preferably carried out in dichloroethane at room temperature with benzaldehyde, sodium triacetoxyborohydride and a catalytic amount of acetic acid for a period of two hours.

30 N-Methylation can, alternatively, be carried out with a source of formaldehyde such as formaldehyde gas, formalin, paraformaldehyde or trioxane and a suitable reducing agent, as described above, in an inert solvent, as described above or, alternatively, in a solvent such as refluxing formic acid without a separate reducing agent. When the source of formaldehyde is trioxane the reaction must be effected in the presence of an acid such as the the formic acid, above. N-Methylation can also be carried out in an inert solvent such as methanol, ethanol or  
35 water in the presence of a source of formaldehyde and a palladium catalyst, such as palladium on carbon, under 1-10 atm. of hydrogen gas for a period of 1-24 hours.

40 Acylation of the secondary nitrogen with either acetyl chloride, acetic anhydride or trifluoroacetic anhydride may be carried out in a suitable inert solvent or mixture of solvents such as methylene chloride, dichloroethane, acetonitrile, toluene, benzene, ethyl acetate, chloroform, ether water or THF. Usually an equivalent of base or an excess of base is used. Bases such as

5 pyridine, triethyl amine, diisopropylethylamine, sodium or potassium carbonate or bicarbonate, hydroxides, imidazole, or dimethylaminopyridine may be used interchangeably. In some or all cases, the base may be used as the solvent as in the case of pyridine or aqueous carbonate solutions. The temperature is not critical but is generally held between -20° C and ambient. The reaction requires 0.5 to 24 hours for completion. Most preferably, the acylating agent is acetic  
10 anhydride or trifluoroacetic anhydride in a solvent such as dichloromethane with a base such as pyridine at 0° C to room temperature for 1 hour.

Referring to Scheme 1 bromination of compound **IV** (or V when R<sup>3</sup> is methyl or benzyl) is carried out in an inert solvent such as methylene chloride, ethyl acetate, chloroform, benzene, toluene, tetrahydrofuran (THF) with a brominating reagent such as bromine, N-bromosuccinimide  
15 (NBS), 1,3-dibromo-5,5-dimethylhydantoin, N-bromoacetamide or similar reagents. The reaction can be carried out at atmospheric pressure with or without a suitable inert base such as sodium, lithium or potassium bicarbonate and tri(C<sub>1</sub>-C<sub>6</sub>)alkylamines such as triethylamine at temperatures between ambient and the reflux temperature of the solvent at atmospheric pressure for a period of 0.5 to 24 hours. It is preferably carried out with NBS in methylene chloride at reflux for 1.5 hours.

20 Chlorination of compound **IV** is effected, under the conditions described above for the bromination reactions including use of the same solvents and water, by treatment with a chlorinating reagent such as chlorine, N-chlorosuccinimide (NCS) and N-chloroacetamide or a similar reagent at temperatures between 0°C and the reflux temperature of the solvent at atmospheric pressure for a period of 0.5 to 24 hours. It is preferably carried out with NCS in  
25 methylene chloride at reflux for 1 - 2 hours or chlorine in water at 0°C for 1 -2 hours.

Iodination of compound **IV** is effected under the conditions described above for chlorination or bromination. This includes the use of the same solvents and water by treatment with an iodinating agent such as N-iodosuccinimide, iodine or ICl or a similar reagent. The iodination is conducted at a temperature between 0° C and the reflux point of the solvent while at  
30 atmospheric pressure for a period of 0.5 - 24 hours. Alternatively it is carried out in methanol or methanol-methylene chloride with a suitable carbonate base such as sodium, potassium, magnesium or calcium carbontes. It is preferably carried out in methanol-methylene chloride with ICl and a base such as calcium carbonate.

The halogenation reactions generally produce a mixture of mono and dihalogenated  
35 products depending upon the exact conditions of time, temperature and reagents. These may be varied to favor a particular substitution pattern as detailed in the experimental section. The mixture can be purified to a single product by crystallization or trituration from a solvent or mixture of solvents such as diethyl ether, isopropylether and ethyl acetate-hexanes. Alternatively, the mixture may be separated by chromatography on silica gel or another support eluting with a  
40 mixture of methylene chloride or chloroform or ethyl acetate with methanol or similarly with

5 mixtures of ethyl acetate with hexanes. It is preferably separated through crystallization from diethyl ether or mixtures of diethyl ether and another solvent such as hexane or by chromatography on silica gel eluting with a mixture of methylene chloride and methanol.

Scheme 2 illustrates the further transformation compound **III**, as exemplified by compound **IIIA**, wherein R<sup>2</sup> is hydrogen and R<sup>1</sup> is bromo or iodo, to the compound of the formula **IIA**.

10 (Although the following procedures are discussed with respect to the compounds of the formulae **IIIA**, **IIA**, and **IA** they are equally applicable to the **B** and **C** counterparts thereof.) Thus, replacement of the bromo or iodo atom by optionally substituted (C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>1</sub>-C<sub>6</sub>)alkenyl or (C<sub>6</sub>-C<sub>10</sub>)aryl may be carried out by reaction of the bromide or iodo or dibromide with an organometallic compound such as tetra(C<sub>1</sub>-C<sub>6</sub>) alkyltin, (C<sub>1</sub>-C<sub>6</sub>)alkenyltri-(C<sub>1</sub>-C<sub>6</sub>)alkyltin or phenyltri(C<sub>1</sub>-C<sub>6</sub>)alkyltin under the influence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium, transbenzylchlorobis (triphenylphosphine)palladium, palladium on carbon, palladium acetate, palladium chloride, palladium trifluoroacetate, palladium trisdibenzylideneacetone, bis (triphenylphosphine)palladium dichloride or other sources of coordinated palladium (0) or palladium (II). The reaction can be carried out in a solvent such as hexamethylphosphoramide (HMPA), N-methylpyrrolidone, ethanol, methanol, water or DMF at temperatures from ambient to 130 °C for 6 - 48 hours at 1-2 atmospheres pressure. Alternatively, the organometallic reagent can be a (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkenyl or arylzinc halide wherein halide refers to chloride, bromide and iodide. The organometallic reagent can also be a (C<sub>1</sub>-C<sub>6</sub>) alkyl ester of a (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkenyl, (C<sub>6</sub>-C<sub>10</sub>)aryl or (C<sub>6</sub>-C<sub>10</sub>)heteroaryl boronic acid. The most preferred conditions involve reaction of the bromide or dibromide with an organotin compound such as tetramethyltin, vinyl(trimethyl)tin, vinyl(tri-n-butyl)tin, phenyl(trimethyl)tin and phenyl(tri-n-butyl)tin in the presence of *trans*-benzylchlorobis(triphenylphosphine)palladium in HMPA at 40 to 80 0°C for 20 to 40 hours. Other preferred conditions for forming the the compound (group) of the formula **II** is by treatment of the compound of formula **III** with the aryl, alkenyl or heteroaryl boronic acid, in a mixture of ethanol and water, in the presence of tetrakis(triphenyl)phosphinepalladium (0) and a suitable base such as sodium, potassium or lithium carbonate or bicarbonate with sodium carbonate generally preferred.

Scheme 4 illustrates the further transformation of compound **III** as exemplified by compound **III-A**, wherein R<sub>2</sub>, R<sub>4</sub> = H and R<sub>1</sub> is bromo or iodo, to the compound of formula **VI**.

35 (Although the following procedures are discussed with respect to the compounds of formulae **IIIA**, and **VI A** they are equally applicable to the **B** and **C** counter parts thereof.) Thus, replacement of the bromo or iodo atom with carboalkoxy or carboxy may be carried out by the reaction of the bromide or the iodo in an alcoholic solvent such as methanol, ethanol, isopropanol, tert-butanol etc or alternatively in water with or without a suitable co-solvent such as DMSO or DMF under 1-200 atmospheres of carbon monoxide gas in the presence of catalytic palladium metal with or without a

5 ligand. Sources of palladium such as palladium on carbon, palladium acetate, palladium chloride, palladium trifluoroacetate, palladium tris(dibenzylideneacetone), palladium bis(dibenzylideneacetone) or other sources of ligated palladium (0) such as tetrakis(triphenylphosphine)palladium or palladium (II) salts such as bis triphenylphosphinepalladium dichloride are effective in this transformation. Suitable ligands for this  
10 transformation are:, 1,3-diphenylphosphinylpropane (dppp), 1,3-diphenylphosphinylethane (dppe), 1,3-diphenylphosphinylbutane (dppb), triphenylphosphine, 2,2'-bis(diphenyl phosphino)-1,1'-binaphthyl (BINAP), 1,1'-bis(diphenylphosphino) ferrocene (dppf) or other commercially available bidentate ligands are satisfactory in this transformation. The reaction was conducted in the presence of a suitable base such as sodium, lithium or potassium carbonate, sodium, lithium or  
15 potassium bicarbonate or sodium, lithium or potassium hydroxides. Temperature of the reaction can vary from room temperature to 100 °C for a time of between 1 and 24 hours. Most preferably the reaction is carried out between iodide or bromide IIIA in methanol with palladium acetate and dppp under 16 psi carbon monoxide and potassium bicarbonate for a period of 16 hrs at 70 °C.

A similar process, as described above for the formation of the ester may be used to  
20 produce the carboxamide of the formula XVIIA from a compound of the formula IIIA (R<sup>1</sup> = I or Br). Thus, replacement of the bromo or iodo atom with a substituted or unsubstituted carboxamide may be carried out by the reaction of the bromide or the iodo under 1-200 atmospheres of carbon monoxide gas in the presence of catalytic palladium metal with or without a ligand using a source of palladium as detailed above. Typically the amine is used as the solvent or if it is a gas then it is  
25 used as a staurated solution in an inert solvent. Preferred conditions, using an amine such as benzyl amine as solvent under 50 psi carbon monoxide at 50 °C in the presence of catalytic bis-triphenylphosphine palladium (II) chloride for 24 hours. Alternatively, the amide XVIIA may be prepared from VIA under standard conditions of ammonolysis or aminolysis with or without a catalyst. Thus a saturated solution of a suitable amine gas in an inert solvent or, if it is a liquid, the  
30 neat amine is heated at atmospheric pressure or at an elevated pressure of from 1-5 atmospheres to produce the amide directly. Alternatively, the reaction may be run under mild conditions using a catalyst such as trialkylaluminum or trialkylstannanes.

The ester or carboxylate VI as well as the carboxamide XVIIA may optionally be further transformed to compounds VII, VIII, IX and X by hydride reduction or by addition of a  
35 organometallic nucleophile. In the case of VII, at least two equivalents of hydride is needed to reduce VI whereas the formation of VIII only requires the addition of one hydride equivalent. Similarly, In the case of X, addition of at least two equivalents of organometallic are needed to afford X whereas addition of a single equivalent will afford IX. Proper control of experimental conditions can afford mono or bis addition of VI and specific conditions for each transformation are  
40 known in the art (for reviews see: O'Neill B.T. in *Comprehensive Organic Synthesis*; B.M. Trost

5 Editor, Vol 1, 397 - 458, Pergamon, 1991 or Reductions in Organic Chemistry, 2nd Ed, Hudlicky, M., ACS Wash. D.C. 1996). Suitable reducing agents for the process VI to VIII and VII are lithium aluminum hydride, sodium, potassium or lithium borohydride, lithium triethylborohydride, diisobutyl aluminum hydride (DiBAL-H), aluminum hydride, amino-borane lithium salt and similar reagents. Generally, these reactions may be conducted in solvents such as THF or diethyl ether, t-  
10 butylmethyl ether, diisopropyl ether, toluene, dichloromethane, dichloroethane or dimethoxyethane. The temperature of the reaction may vary but can be run between - 78 ° C and ambient temperature or between ambient temperature and the reflux point of the solvent. The reaction generally requires between 0.5 and 24 hours for completion and generally is run at ambient pressure. Most preferred conditions are DIBAL-H in methylene chloride at - 78 ° C for 3  
15 hours.

Suitable organometallic reagents for the process of VI to IX and X as well as XVII to IX include (C1-C6)alkyl lithiums, (C1-C6)alkyl magnesium halides (wherein halide refers optionally to chloride, bromide or iodide), or (C1-C6)alkyl cuprate or di(C1-C6)alkyl cuprates. More specifically methyl lithium, methyl magnesium halide, t-butyl lithium, t-butyl magnesium halide, isopropyl lithium, isopropyl magnesium halide, n-butyl lithium, n-butyl magnesium halide, s-butyl lithium, s-butyl magnesium halide. Most specifically methyl lithium and methyl magnesium halide. The reaction can be run in several inert solvents such as THF or diethyl ether, dimethoxyethane or similar solvents. The temperature of the reaction may vary but can be run between - 78 ° C and ambient temperature or between ambient temperature and the reflux point of the solvent. The reaction generally requires between 0.5 and 24 hours for completion and generally is run at ambient pressure. The compound of formula X may also be transformed into compounds of this invention by modification of the tertiary alcohol. For example, the compound of formula IX may be obtained through the sequence X to XI to XII followed by conversion directly to IX. This sequence may be completed with or without isolation of the individual intermediates which are themselves a part of the subject matter of this case. Transformation of X to XI may be carried out under acidic conditions or alternatively by first transforming the tertiary alcohol to a suitable leaving group such as a halogen or a group such as a mesylate, triflate, tosylate or other suitable activating group followed by base catalyzed elimination. The reaction under acidic conditions may use one of the following acidic reagents in water with or without a co-solvent: acetic, trifluoroacetic, sulfuric, hydrochloric, hydrobromic acid and other similar reagents or alternatively silica gel may be used. Suitable solvents include water, methanol, ethanol, isopropanol, THF or diethyl ether, t-butylmethyl ether, diisopropyl ether, toluene, dichloromethane, dichloroethane chloroform or dimethoxyethane, ethyl acetate acetonitrile or similar solvents or combination of solvents. The transformation from X to XI may be completed at a temperature of 0° C to room temperature for a period of 5 minutes to 40 5 hours. The most preferred conditions are trifluoroacetic acid in methylene chloride at 0° C to

5 room temperature for a period of two hours.

Conversion of XI to IX may be carried out with or without isolation of the intermediate XII. Formation of XII can be accomplished with a reagent such as osmium tetroxide or potassium permanganate in a suitable solvent or combination of solvents such as water, acetone, t-butanol, dioxane or THF. The osmium tetroxide can be used in catalytic quantities if combined with a 10 second oxidant such as N-methylmorpholine-N-oxide or trimethyl amine N-oxide, triethylamine-N-oxide or sodium periodate. Generally the reaction is carried out at room temperature but may be run between 0° C and the reflux point of the solvent for a period of 12 to 48 hours. The most preferred conditions involve the use of catalytic osmium tetroxide with N-methylmorpholine-N-oxide and sodium periodate in dioxane / water at room temperature for 24 hours to afford IX 15 directly. Alternatively, XI may be directly converted to IX with ozone gas under standard conditions. Thus ozone in oxygen may be introduced to a solution of XI in a suitable solvent such as methanol, ethanol, isopropanol, toluene, dichloromethane, dichloroethane chloroform, ethyl acetate and acetonitrile or similar solvents or combination of solvents. The reaction is generally run at - 78 ° C but may also be run between - 78 ° C to ambient temperature for a period of 5 20 minutes to 1 hour. An indicator such as sudan red may or may not be employed to indicate when the reaction is complete. The reaction is then quenched under reducing conditions to afford the product IX. Suitable reducing agents include but are not limited to dimethyl sulfide, zinc and acetic acid, hydrogen / palladium on carbon, triphenyl phosphine or similar reagents. The most preferred conditions are ozone in methylene chloride at - 78 ° C in the presence of sudan red indicator 25 followed by addition of dimethyl sulfide.

Direct conversion of III A (R<sub>1</sub> = Br or I) to IX may also be accomplished through halogen metal exchange and acylation. Thus the bromide or iodide IIIA may be treated with a metal such as lithium, sodium, magnesium or zinc to form the corresponding organometallic which is then quenched with a suitable acylating agent. Suitable acylating agents include esters, thioesters, 30 acids, amides, N-methoxy-N-methylamides, anhydrides, acid chlorides and similar agents. The reaction may be initiated by using the metal directly or by prior formation of a metal complex with an aromatic agent such as naphthalene or biphenyl such as lithium naphthalide or through the use of an organometallic such as n-butyl lithium, t-butyl lithium, s-butyl lithium, methyl magnesium halide or similar reagents. Suitable solvents for this transformation include THF, ether, 35 dimethoxyethane as well as similar reagents. The most preferred conditions are n-butyl lithium in THF at - 78 ° C to 0° C using N-methoxy-N-methylamides for 2.5 hours.

Direct conversion of VIIIA to IX A may be accomplished as described above for the conversion of VIA to IX A, however, a second step is required to convert the intermediate secondary alcohol (not shown) in to the ketone. Suitable reagents for this transformation include 40 chromium trioxide and chromium trioxide pyridine complex, pyridium chlorochromate, pyridium

5 dichromate, potassium permanganate, hypochlorous acid, mixtures of DMSO with oxalyl chloride or trifluoracetic anhydride and other well known reagents capable of oxidation of alcohols to ketones.

Scheme 5 illustrates the further transformation of compound III as exemplified by compound III A, wherein R2, R4 = H and R1 is bromo or iodo, to the compounds of formula XIII, XIV, XV, XVI. (Although the following procedures are discussed with respect to the compounds of formulae IIIA, and XIII A, XIV A, XV A, XVI A they are equally applicable to the B and C counter parts thereof.) Thus, replacement of the bromo or iodo atom with zinc cyanide afforded XIII (X = N) under palladium catalysis in a polar aprotic solvent such as DMF, DMSO, N,N-dimethylacetamide, N-methyl pyrrolidone or similar solvents at a temperature between ambient 10 temperature and 150 °C for a period of 6 to 48 hours at atmospheric pressure. Suitable catalysis include but are not limited to palladium tris(dibenzylideneacetone), palladium bis(dibenzylideneacetone) or other sources of ligated palladium (0) such as tetrakis(triphenylphosphine)palladium or palladium (II) salts such as bis(triphenylphosphine)palladium dichloride:, 1,3-diphenyl phosphinylpropane palladium(0) [(dppp)Pd(0)], 1,3-diphenylphosphinyl 15 ethane palladium(0) [(dppe)Pd(0)], 1,3-diphenylphosphinylbutanepalladium(0) [(dppb) Pd(0)], 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl palladium(0) [(BINAP) Pd(0)], 1,1'-bis(diphenylphosphino) ferrocene palladium(0) [(dpfp) Pd(0)] or other commercially available palladium sources are 20 satisfactory in this transformation. The most preferred conditions use bromo or iodo IIIA together with zinc cyanide in DMF and tetrakis(triphenylphosphine)palladium (0) at 80 °C for 16 hours.

25 Alternatively, in a similar manner to that described above, one may replace the bromo or iodo atom with an acetylene to afford XIII (X = CR, wherein R = H, (C<sub>1</sub> - C<sub>6</sub>) alkyl, aryl including substituted alkyl, aryl). Thus treatment as above but with the substitution of an acetylene (such as trimethylsilylacetylene or other acetylenes) for zinc cyanide will lead to the formation of XIII (X = CR). Typically the reaction is run in a solvent such as diethylamine or pyrrolidine or other 30 secondary amines with a catalyst such as copper (I) iodide, bromide or chloride and in the presence of a palladium catalyst as described above. The reaction is run at a temperature between ambient temperature and the reflux point of the solvent for a period of 1 to 24 hours at atmospheric pressure. Typically it is run at ambient temperature for 4 hours.

Substitution of the bromo or iodo atom in III A with a primary or secondary amine R,R'NH, 35 wherein R and R' may be any of H, (C<sub>1</sub> - C<sub>6</sub>) alkyl, aryl and benzyl, to afford XIV. Typically, the reaction is conducted in a solvent such as toluene, benzene, xylene, dioxane or THF at a temperature between ambient temperature and the reflux point of the solvent. Typically the reaction is conducted in toluene at about 80 °C. The reaction is catalyzed with palladium metal in the presence of a suitable ligand. Sources of palladium include but are not limited to palladium 40 acetate, palladium tris(dibenzylideneacetone), palladium bis(dibenzylideneacetone), in the

5 presence of a ligand such as dppp, dppe, dppb, dppf, BINAP, tri-o-tolylphosphine or alternatively tetrakis(triphenylphosphine)palladium, 1,3-diphenylphosphinyl propanepalladium (0) [(dppp)Pd(0)], 1,3-diphenylphosphinyl ethane palladium(0) [(dppe)Pd(0)], 1,3-diphenylphosphinylbutane palladium(0) [(dppb)Pd(0)], 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl palladium(0) [(BINAP) Pd(0)], 1,1'-bis(diphenylphosphino) ferrocene palladium(0) [(dppf) Pd(0)] or other commercially 10 available palladium sources are satisfactory in this transformation. Most preferably 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl palladium(0) [(BINAP) Pd(0)] is used. Typically a base such as sodium, potassium or lithium butoxide or sodium, potassium tert-amyloxide is used in the process. Most preferably sodium t-butoxide is used.

Substitution of the bromo or iodo atom in III A with a sulfide RSH, wherein R may be any 15 of H, (C<sub>1</sub> - C<sub>6</sub>) alkyl, aryl and benzyl, to afford XVI (wherein n = 0,1,2). Typically, the reaction is conducted in a solvent such as toluene, benzene, xylene, dioxane or THF at a temperature between ambient temperature and the reflux point of the solvent. Typically the reaction is conducted in toluene at about 80 °C. The reaction is catalyzed with palladium metal in the presence of a suitable ligand. Sources of palladium include but are not limited to palladium 20 acetate, palladium tris(dibenzylideneacetone), palladium bis(dibenzylideneacetone), in the presence of a ligand such as triphenylphosphine, dppp, dppe, dppb, dppf, BINAP, tri-o-tolylphosphine or alternatively tetrakis(triphenylphosphine)palladium, 1,3-diphenylphosphinyl propanepalladium (0) [(dppp)Pd(0)], 1,3-diphenylphosphinyl ethane palladium(0) [(dppe)Pd(0)], 1,3-diphenylphosphinylbutane palladium(0) [(dppb)Pd(0)], 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl palladium(0) [(BINAP) Pd(0)], 1,1'-bis(diphenylphosphino) ferrocene palladium(0) [(dppf) Pd(0)] or other commercially 25 available palladium sources are satisfactory in this transformation. Most preferably 1,3-diphenylphosphinyl ethane palladium(0) [(dppe)Pd(0)], is used. Oxidation of the newly formed sulfide (wherein n= 0) to afford the sulfoxide (wherein n= 1) or the sulfone (wherein n= 2), may be accomplished under standard conditions for oxidation known in 30 the art. Typically, oxidants such as oxygen, hydrogen peroxide, OXONE, m-chloroperbenzoic acid or other per-acids such as peracetic acid and hypochlorous acid may be used.

Alternatively, substitution of the bromo or iodo atom in III A may be conducted with an alkene or a suitable vinyl ether to form XV A. The olefin or vinyl ether may be part of a ring system or alternatively, it may be part of an acyclic system. Thus R in XV may be simply (C<sub>1</sub> - C<sub>6</sub>) alkyl or 35 benzyl or alternatively it may be part of a ring which includes the olefin. The ring size typically contains 5,6,7 or 8 atoms. The reaction is conducted in a suitable polar aprotic solvent such as DMF, DMSO, N,N-dimethylacetamide, N-methyl pyrrolidone or similar solvents at a temperature between ambient temperature and 150 °C for a period of 0.5 to 24 hours at atmospheric pressure. Typically the reaction is conducted in DMF at about 90 °C. The reaction is catalyzed by palladium 40 typically in the form of palladium acetate or palladium dichloride with or without a ligand such as

5 triphenylphosphine, dppp, dppe, dppb, dppf, BINAP, tri-o-tolylphosphine. The reaction may also be run in the presence or absence of a suitable base such as sodium, lithium or potassium acetate, triethyl amine or diisopropylethylamine and alternatively in the presence or absence of teraalkyl ammonium salts such as terabutylammonium chloride, bromide, acetate or iodide. Typically the reaction is conducted between IIIA and dihydrofuran in DMF at about 90 °C with

10 palladium acetate, triphenyl phosphine, tera-butyl ammonium acetate, potassium acetate for 16 hours. Also the reaction between III A and butyl vinyl ether is conducted in DMF at 90 °C for 1.5 hours using palladium acetate, dppf and triethyl amine. The resulting product retains the olefin carbon bond which may undergo further reaction under standard conditions known in the art. These include but are not limited to hydrogenation and also reaction with aqueous acid.

15 The t-BOC protecting group can be readily removed from the protected products IIIA, IIA, VIA, VIIA, VIIIA, IXA, XA, XIA, XIIA, XVIIA, XVIIIA, XIVA, XVA, and XVIA described above, to form the compound IA (Scheme 2) wherein R<sup>3</sup> is hydrogen and R<sup>1</sup> is as defined previously respectively, by treatment with an acid such as hydrochloric, sulfuric, trifluoroacetic, acetic, nitric, hydrofluoric, hydrobromic and hydroiodic using water as a solvent or co-solvent or in anhydrous

20 organic solvents such as methanol, ethanol, ether, ethyl acetate, methylene chloride and chloroform or mixtures thereof. The product is obtained as its acid salt which may be then treated with a suitable base including, but not limited to, the following: sodium, lithium and potassium carbonates, bicarbonates and hydroxides, generally, in water to afford the desired material as the free base form.

25 The benzyl and CBZ protecting groups can be removed from the compounds of formulae IIIA, IIA, VIA, VIIA, VIIIA, IXA, XA, XIA, XIIA, XVIIA, XIIIA, XIVA, XVA and XVIA by treatment, in a solvent such as methanol, water, acetic acid and ethyl acetate, with 1 to 10 atmospheres of hydrogen gas in the presence of a catalyst such as palladium on carbon, palladium hydroxide and palladium hydrochloride, at a temperature from ambient to about 50°C.

30 Compound IA, wherein R<sup>3</sup> is hydrogen, can be treated, as described above for N protection, by benzylation or methylation, to form compound IA wherein R<sup>3</sup> is benzyl or methyl. Alternatively, if R<sup>3</sup>, in compound IA, is to be benzyl or methyl and the protecting group P is benzyl or methyl no deprotection step is needed as compound IA corresponds to compound IIIA, IIA, VIA, VIIA, VIIIA, IXA, XA, XIA, XIIA, XVIIA, XIIIA, XIVA, XVA and XVIA. If P is an acyl group

35 such as a trifluoroacetyl group then it may be removed by treatment with dilute acid or base to afford a compound of the formula I. Thus treatment with aqueous sodium bicarbonate, carbonate or hydroxide and a co-solvent such as methanol, ethanol, THF, dioxane or similar inert solvents may be used. Also methanol and sodium methoxide may be used. Alternatively, aqueous acid such as dilute hydrochloric acid may be used in combination with an inert co-solvent as described

40 above. The temperature of the reaction may range from 0° C to the reflux point of the solvent.

5. The compounds of the formula I and their pharmaceutically acceptable salts (hereafter "the active compounds") can be administered via either the oral, transdermal (e.g., through the use of a patch), intranasal, sublingual, rectal, parenteral or topical routes. Transdermal and oral administration are preferred. These compounds are, most desirably, administered in dosages ranging from about 0.25 mg up to about 1500 mg per day, preferably from about 0.25 to about 300

10 mg per day in single or divided doses, although variations will necessarily occur depending upon the weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 0.02 mg to about 10 mg per kg of body weight per day is most desirably employed. Variations may nevertheless occur depending upon the weight and condition of the persons being treated and their individual responses to said

15 medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval during which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects, provided that such larger doses are first divided into several small doses for administration throughout the day.

20 The active compounds can be administered alone or in combination with pharmaceutically acceptable carriers or diluents by any of the several routes previously indicated. More particularly, the active compounds can be administered in a wide variety of different dosage forms, e.g., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, transdermal patches, lozenges, troches, hard candies, powders, sprays, creams,

25 salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents. In addition, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the active compounds are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

30 For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate,

35 sodium lauryl sulfate and talc can be used for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar] as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration the active ingredient may be combined with various sweetening or flavoring agents, coloring matter and, if so desired,

5 combined with various sweetening or flavoring agents, coloring matter and, if so desired, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

For parenteral administration, a solution of an active compound in either sesame or peanut oil or in aqueous propylene glycol can be employed. The aqueous solutions should be 10 suitably buffered (preferably pH greater than 8), if necessary, and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

15 It is also possible to administer the active compounds topically and this can be done by way of creams, a patch, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

#### Biological Assay

20 The effectiveness of the active compounds in suppressing nicotine binding to specific receptor sites is determined by the following procedure which is a modification of the methods of Lippiello, P. M. and Fernandez, K. G. (in The Binding of L-[<sup>3</sup>H]Nicotine To A Single Class of High-Affinity Sites in Rat Brain Membranes, Molecular Pharm., 29, 448-54, (1986)) and Anderson, D. J. and Arneric, S. P. (in Nicotinic Receptor Binding of <sup>3</sup>H-Cystisine, <sup>3</sup>H-Nicotine and <sup>3</sup>H-Methylcarmabamylcholine In Rat Brain, European J. Pharm., 253, 261-67 (1994)).

25 Procedure

Male Sprague-Dawley rats (200-300 g) from Charles River were housed in groups in hanging stainless steel wire cages and were maintained on a 12 hour light/dark cycle (7 a.m.-7 p.m. light period). They received standard Purina Rat Chow and water *ad libitum*.

30 The rats were killed by decapitation. Brains were removed immediately following decapitation. Membranes were prepared from brain tissue according to the methods of Lippiello and Fernandez (Molec Pharmacol, 29, 448-454, (1986) with some modifications. Whole brains were removed, rinsed with ice-cold buffer, and homogenized at 0° in 10 volumes of buffer (w/v) using a Brinkmann Polytron™, setting 6, for 30 seconds. The buffer consisted of 50 mM Tris HCl at a pH of 7.5 at room temperature. The homogenate was sedimented by centrifugation (10 minutes; 50,000 x g; 0 to 4°C. The supernatant was poured off and the membranes were gently resuspended with the Polytron and centrifuged again (10 minutes; 50,000 x g; 0 to 4°C. After the second centrifugation, the membranes were resuspended in assay buffer at a concentration of 1.0g/100mL. The composition of the standard assay buffer was 50 mM Tris HCl, 120 mM NaCl, 5 mM KCl, 2 mM MgCl<sub>2</sub>, 2 mM CaCl<sub>2</sub> and has a pH of 7.4 at room temperature.

5        Routine assays were performed in borosilicate glass test tubes. The assay mixture typically consisted of 0.9 mg of membrane protein in a final incubation volume of 1.0 mL. Three sets of tubes were prepared wherein the tubes in each set contained 50 $\mu$ L of vehicle, blank, or test compound solution, respectively. To each tube was added 200  $\mu$ L of [<sup>3</sup>H]-nicotine in assay buffer followed by 750  $\mu$ L of the membrane suspension. The final concentration of nicotine in each tube  
10      was 0.9 nM. The final concentration of cytisine in the blank was 1  $\mu$ M. The vehicle consisted of deionized water containing 30  $\mu$ L of 1 N acetic acid per 50 mL of water. The test compounds and cytisine were dissolved in vehicle. Assays were initiated by vortexing after addition of the membrane suspension to the tube. The samples were incubated at 0 to 4° C in an iced shaking water bath. Incubations were terminated by rapid filtration under vacuum through Whatman  
15      GF/B™ glass fiber filters using a Brandel™ multi-manifold tissue harvester. Following the initial filtration of the assay mixture, filters were washed two times with ice-cold assay buffer (5 mL each). The filters were then placed in counting vials and mixed vigorously with 20 mL of Ready Safe™ (Beckman) before quantification of radioactivity. Samples were counted in a LKB Wallach Rackbeta™ liquid scintillation counter at 40-50% efficiency. All determinations were in triplicate.

20      Calculations

Specific binding (C) to the membrane is the difference between total binding in the samples containing vehicle only and membrane (A) and non-specific binding in the samples containing the membrane and cytisine (B), i.e.,

$$\text{Specific binding} = (C) = (A) - (B).$$

25      Specific binding in the presence of the test compound (E) is the difference between the total binding in the presence of the test compound (D) and non-specific binding (B), i.e., (E) = (D) - (B).

$$\% \text{ Inhibition} = (1 - (E)/(C)) \times 100.$$

30      The compounds of the invention, which were tested, exhibited IC<sub>50</sub> values of less than 1  $\mu$ M.

Preparation

N-t-BOC-cytisine (N-t-BOC-cytisine)

To a one liter round bottom flask was charged 10 gm (0.053 mmol) (−)-cytisine followed by a mixture of 320 mL methylene chloride and 100 mL water. The two phase mixture was treated with  
35      6.62 gm (0.079 mmol) sodium bicarbonate and finally 12.6 gm (0.058 mmol) di-t-butyl-dicarbonate. The reaction mixture was heated under reflux for 1.5 hours. The mixture was allowed to cool and was then diluted with brine. The organic layer was washed with brine and dried and the solvent evaporated. There was obtained 14.4 gm (94 % crude) of the title product which was used directly in the next step. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  7.28 (dd, 1H), 6.45 (d, 1H), 6.05 (d, 1H), 4.19 (m,

5 3H), 3.81 (dd, 1H), 3.0 (br.s, 3H), 2.41 (br.s, 1H), 1.99 (m, 2H), 1.29 (br.s, 9H) ppm; mass spectrum (thermospray) m/e 291 p+1.

Example 1

N-t-BOC-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one (9-bromo-t-BOC cytisine)

10 To a 250 ml round bottom flask was added 1.87 gm (6.4 mmol) of t-BOC cytisine in 100 ml of methylene chloride. The solution was treated with 1.14 gm (6.4 mmol) of N-bromosuccinimide (NBS) and the reaction mixture was heated under reflux for 1.5 hours. The mixture was allowed to cool to room temperature and was diluted with water. The organic phase was separated, washed with brine, dried and the solvent was then evaporated in vacuo. The 15 residue was flash chromatographed on silica gel eluting with methylene chloride:methanol (99:1). Three products were obtained. The least polar material was identified as the 9,11-dibromo t-BOC-cytisine. The most polar material was identified as 11-bromo-t-BOC-cytisine. The second material to elute, of intermediate polarity, was the title product 9-bromo-t-BOC-cytisine 1.34 gm (57%)

16 9-Bromo-t-BOC-cytisine:  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  7.68 (s, 1H) 5.99 (s, 1H), 4.28 (d, 1H), 4.20 (br, 2H), 3.89 (dd, 1H), 3.00 (br.s, 3H), 2.42 (br. s, 1H), 1.98 (br.s, 2H), 1.31 (s, 9H) ppm; mass spectrum (thermospray) m/e 369, 371

17 9,11-Dibromo-t-BOC-cytisine:  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  7.88 (s, 1H), 4.38, (br.s, 2H), 4.25 (d, 1H), 3.90 (dd, 1H), 3.45 (br.s, 1H), 3.00 (br. m, 2H), 2.45 (br.s, 1H), 2.00 (br.s, 2H), 1.29 (br.s, 9H) ppm; mass spectrum (thermospray) m/e 447, 449, 451 p+1, p+2, p+4.

22 11-Bromo-t-BOC-cytisine:  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  7.40 (d, 1H), 6.38 (d, 1H), 4.36 (br.d, 2 H), 4.15 (d, 1H), 3.82 (dd, 1H), 3.40 (br.s, 1H), 2.96 (br.m, 2H), 2.40 (br.s, 1H), 1.98 (s, 2H), 1.25 (br.s, 9H) ppm; mass spectrum (thermospray) m/e 369, 371

Example 2

9-Bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one

28 hydrochloride salt (9-bromocytisine)

A solution of the title product of Example 1 (1.28 gm; 3.5 mmol) in ethyl acetate (10 ml) was treated with a solution of 3 M HCl(g) in ethyl acetate. After 30 minutes a precipitate began to form. The reaction mixture was granulated for 24 hours to enhance the quality of the crystalline product. After filtration and drying *in vacuo* there was obtained 0.92 gm (87%) of the title product.

33 An analytical sample was prepared by recrystallization from methanol-ether. The free base was prepared by treatment of the hydrochloride with methylene chloride and a 12N NaOH solution.

mp (uncorrected, Thomas-Hoover Capillary apparatus) > 270 °C.

$^1\text{H}$  NMR (free base, CDCl<sub>3</sub>, 250 MHz)  $\delta$  7.58 (d, 1H), 5.87 (d, 1H), 4.06 (d, 1H), 3.83 (dd, 1H), 2.92 (m, 5H), 2.27 (m, 1H), 1.87 (br. s, 2H) ppm [?].

5  $^{13}\text{C}$  NMR (free base,  $\text{CDCl}_3$ , 100.1 MHz)  $\delta$  160.0, 151.0, 140.7, 112.0, 104.9, 53.8, 52.9, 51.1, 35.4, 27.6, 26.1 ppm.

<sup>1</sup>H NMR (hydrochloride salt, D<sub>2</sub>O, 250 MHz) δ 8.03 (d, 1H), 6.5 (d, 1H), 4.28 (d, 1H), 4.1 (dd, 1H), 3.5 (m, 5 H), 2.88 (m, 1H), 2.15 (m, 2H) ppm.

<sup>13</sup>C NMR (hydrochloride salt, D<sub>2</sub>O, 100.1 MHz) δ 160.9 (C=O), 146.8 (C-Br), 143.1 (C-H)

10 112.1 (-C-), 109.5 (C-H), 50.0 (CH<sub>2</sub>), 49.2 (CH<sub>2</sub>), 48.2 (CH<sub>2</sub>), 31.4, 24.8 (CH), 22.4 (CH) (CH<sub>2</sub>) ppm..

Optical Rotation  $[\alpha]_D = -55.9^\circ$   $c = 0.63$ , methanol

mass spectrum (thermospray) m/e 269, 271

Analytical for  $C_{11}H_{13}BrN_2O \cdot HCl \cdot 0.5 H_2O$  Calc: C, 41.99; H, 4.81; N, 8.90; Found: C, 41.80; H, 5.05; N, 8.88.

The compounds of Examples 3 and 4 were prepared according to the method of Example

2.

### Example 3

## 11-Bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one

20  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 250 MHz)  $\delta$  7.4 (d, 1H), 6.36 (d, 1H), 4.05 (d, 1H), 3.89 (dd, 1H), 3.32 (br.s, 1H), 3.22 - 2.85 (m, 4H), 2.32 (br.s, 1H), 1.95 (br.m, 3H) ppm; mass spectrum (thermospray) m/e 269, 271.

#### Example 4

### 9,11-Dibromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one

25 hydrochloride salt

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz) δ 7.89 (s, 1H), 4.19 (d, 1H), 3.96 (dd, 1H), 3.39 (br.s, 1H), 3.23 (dd, 2H), 3.03 (dd, 2H), 2.78 (br.s, 1H), 2.41 (br.s, 1H), 2.00 (m, 2H) ppm; mass spectrum (particle beam) m/e 347, 349, 351.

### Example 5

30 **N-t-BOC-9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one**

(9-chloro-t-BOC-cytisine) and N-t-11-chloro-1,2,3,4,5,6-hexahydro-1,5-methanopyrido[1,2-a][1,5]diazocin-8-one (11-chloro-t-BOC-cytisine)

To a 50 ml round bottom flask was added 1.19 gm (4.1 mmol) of t-BOC cytisine in 25 ml of methylene chloride. To the above solution was added 0.55 gm (4.1 mmol) of N-chlorosuccinimide and the reaction mixture was heated to reflux for 16 hrs. The reaction mixture was allowed to cool to room temperature and was then diluted with water. The organic phase was separated, washed with brine, dried and the solvent was then evaporated in vacuo. The residue was flash chromatographed on silica gel eluting with methylene chloride : methanol (98:2). Two compounds were obtained. The least polar material was identified as 9-chloro-t-BOC-cytisine (0.062 gm) and the second material to elute was 11-chloro-t-BOC-cytisine (0.914 gm)

5        9-Chloro-t-BOC-cytisine:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 250 MHz)  $\delta$  7.46 (d, 1H), 6.04 (d, 1H), 4.26 (d, 1H), 4.19 (br.m, 2H), 3.85 (dd, 1H), 3.05 (br.m, 3H), 2.43 (br.s, 1H), 1.98 (br.s, 2H), 1.28 (br.m, 9H) ppm; mass spectrum  $m/e$  325 p+1.

10        11-Chloro-t-BOC-cytisine:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 250 MHz)  $\delta$  7.34 (d, 1H), 6.46 (d, 1H), 4.37 (br.m, 2H), 4.19 (d, 1H), 3.84 (dd, 1H), 3.49 (br.m, 1H), 3.01 (m, 2H), 2.46 (br.s, 1H), 2.00 (br.s, 2H), 1.29 (br.m, 9H) ppm; mass spectrum (particle beam) 325 p+1.

Example 6

9-Chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one hydrochloride salt. (9-chloro-cytisine, HCl salt)

An excess of a solution of 3 M HCl (g) in ethyl acetate was added to the least polar product of Example 5 (0.063 gm; 0.19 mmol) in excess ethyl acetate. After 30 minutes a precipitate began to form. The reaction mixture was granulated for 24 hours to enhance the quality of the crystalline product. After filtration and 10 minutes drying in vacuo there was obtained 0.041 gm (95%) of the title product.  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 250 MHz)  $\delta$  7.61 (d, 1H) 6.34 (d, 1H), 4.06 (d, 1H), 3.88 (dd, 1H), 3.25 (m, 4H), 2.66 (br.s, 1H), 1.93 (dd, 2H) ppm, mass spectrum (thermal spray) 225 p+1.

Example 7

11-Chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one hydrochloride salt. (11-chlorocytisine, HCl salt)

An excess of 3 M HCl (g) in ethyl acetate was added to the more polar product of Example 5 (0.079 gm; 0.24 mmol) in ethyl acetate. After 30 minutes a precipitate began to form. The reaction mixture was granulated for 24 hours to enhance the quality of the crystalline product. After filtration and brief (10 min) drying in vacuo there was obtained 0.050 gm of the title product. An analytical sample was prepared by recrystallization from methanol-ether.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 250 MHz)  $\delta$  7.30 (d, 1H), 6.43 (d, 1H), 4.08 (d, 1H), 3.89 (dd, 1H), 3.38 (br.s, 1H), 3.20 - 2.85 (m, 4H), 2.35 (br.s, 1H), 1.95 (m, 2H) ppm; mass spectrum (thermal spray) 225 p+1

Example 8

9,11-Dichloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one (9,11-dichlorocytisine)

To a 10 ml round bottom flask was added 0.2 gm (0.69 mmol) of t-BOC-cytisine in 3 ml of water and the solution was cooled in an ice bath. The solution was treated with 2 ml of water saturated with chlorine gas and stirred for 1.5 hours. The reaction mixture was diluted with 2N NaOH and extracted with methylene chloride. The organic phase was washed with brine, dried and the solvent was then evaporated in vacuo. The residue (210 mg) was used directly in the reaction that follows.

5 To a 35 ml round bottom flask was added the above product (0.21 gm) and 12 ml of 1:1 dioxane : ethyl acetate. The solution was saturated with HCl gas until a white precipitate formed. The mixture was heated under reflux for 2 hours. After cooling to room temperature the reaction mixture was diluted with methylene chloride and treated with 2 N NaOH solution. The organic phase was washed with brine, dried and the solvent was evaporated in vacuo. The residue was  
10 flash chromatographed on silica gel eluting first with methylene chloride, methanol (96:4) followed by elution with 95:5 methylene chloride:methanol. Two compounds were obtained. The least polar (first to elute) material was identified as 9,11-dichlorocytisine (65 mg) and the second, i.e., the more polar, material to elute was 11-chlorocytisine (40 mg) (also prepared above). Both compounds were converted into the HCl salts with HCl (g) in ether:ethanol 10:1.  
15 9,11-Dichlorocytisine:  $^1\text{H}$  NMR (Free Base,  $\text{CDCl}_3$ , 250 MHz)  $\delta$  7.55 (s, 1H), 4.15 (d, 1H), 3.95 (dd, 1H), 3.38 (br.s, 1H), 3.20 - 2.89 (m, 4H), 2.38 (br.s, 1H), 1.95 (m, 2H) ppm ; mass spectrum (particle beam) 259.

Example 9

N-t-BOC-9-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one  
20 (N-t-BOC-9-methylcytisine)

To a 6 ml round bottom flask was added 0.132 gm (0.36mmol) of 9-bromo-t-BOC-cytisine (the title product of Example 1) and 1.5 ml of hexamethylphosphoramide (HMPA). The solution was treated with 0.043 gm (0.057mmol) of *trans*-benzylchloro-bis(triphenylphosphine)palladium and 0.153 ml (1.1mmol) tetramethyltin. The reaction mixture was heated at 65° C for 30 hours.  
25 The dark reaction mixture was partitioned between 1:1 ethyl acetate : hexanes and 50 % brine. The organic phase was washed with brine, dried and the solvent evaporated. The residue was chromatographed on silica gel eluting with 1% methanol in methylene chloride. There was obtained 50 mg (45%) of the title product which was used directly in the next step.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 250 MHz)  $\delta$  7.15 (d, 1H), 5.98 (d, 1H), 4.45 - 4.00 (m, 2H), 4.22 (d, 1H), 3.80 (dd, 1H),  
30 2.98 (m, 3H), 2.39 (br.s, 1H), 2.09 (s, 3H), 1.92 (br.s, 2H) 1.28 (br.s, 9H) ppm; mass spectrum (ACPI) 305 p+1; 205 (p-t-BOC).

Example 10

9-Methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one  
hydrochloride salt (9-methyl-cytisine, HCl salt)

35 The title product of Example 9 (0.050 gm; 0.16 mmol) in ethyl acetate was treated with an excess of a solution of 3 M HCl (g) in ethyl acetate. The reaction mixture was stirred for 1 hour and then partitioned between 2 N NaOH (aq) and methylene chloride. The organic layer was washed with brine, dried and the solvent evaporated. The residue was chromatographed on silica gel (elution with 2% methanol in methylene chloride with 0.5 % ammonium hydroxide). The  
40 recovered product was then treated, in methanol-ether, with HCl gas. After filtration and 10

5 minutes drying in vacuo there was obtained 25 mg of the title product. An analytical sample was prepared by recrystallization from methanol - ether.  $^1\text{H}$  NMR (Free Base,  $\text{CDCl}_3$ , 250 MHz)  $\delta$  7.18 (d, 1H), 5.92 (d, 1H), 4.18 (d, 1H), 3.89 (dd, 1H), 3.04 (m, 4H), 2.87 (br.s, 1H), 2.30 (br.s, 1H), 2.12 (s, 3H), 1.92 (br.s, 2H) ppm; mass spectrum (APCI) 205 p+1.

Example 11

10 N-t-BOC-11-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one  
(N-t-BOC-11-methyl-cytisine, HCl salt)

To a 5 ml Wheaton flask was added 0.030 gm (0.081 mmol) of 11-bromo-t-BOC-cytisine (as prepared in Example 1) and 0.5 ml of HMPA. The solution was treated with 0.009 gm (0.01 mmol) of *trans*-benzylchloro-bis(triphenylphosphine)palladium and 0.035 ml (0.25 mmol) 15 tetramethyltin. The reaction mixture was heated at 65°C for 42 hours. The dark reaction mixture was partitioned between 1:1 ethyl acetate : hexanes and 50 % brine. The organic phase was washed with brine and the solvent was then evaporated. The residue was chromatographed on silica gel eluting first with ethyl acetate followed by 1% methanol in ethyl acetate. There was obtained 20 mg (81%) of the title product which was used directly in the next step.  $^1\text{H}$  NMR (20  $\text{CDCl}_3$ , 250 MHz)  $\delta$  7.18 (d, 1H), 6.45 (d, 1H), 4.46 - 4.10 (m, 2H), 4.22 (d, 1H), 3.87 (dd, 1H), 3.05 (m, 3H), 2.40 (br.s, 1H), 2.12 (s, 3H), 1.98 (m, 2H) 1.26 (br.s, 9H) ppm; mass spectrum (thermospray) 305 p+1.

Example 12

25 11-Methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one  
hydrochloride salt (11-methyl-cytisine, HCl salt)

The title product of Example 11 (0.020 gm; 0.065 mmol) in ethyl acetate was treated with excess 3 M HCl (g) in ethyl acetate. The reaction mixture was stirred for 1 hour and was then partitioned between 2 N NaOH solution and methylene chloride. The organic layer was washed with brine, dried and the solvent evaporated. The residue was chromatographed on silica gel 30 (elution with 1% methanol in methylene chloride). The recovered desired product was then treated, in methanol-ether, with HCl gas. Upon filtration and brief drying in vacuo there was obtained 6 mg of the title product. An analytical sample was prepared by recrystallization from methanol : ether 1:10.  $^1\text{H}$  NMR (Free Base,  $\text{CDCl}_3$ , 250 MHz)  $\delta$  7.20 (d, 1H), 6.45 (d, 1H), 4.18 (d, 1H), 3.95 (dd, 1H), 3.05 (m, 5H), 2.31 (br.s, 1H), 2.10 (s, 3H), 1.98 (m, 2H) ppm; mass spectrum (thermospray) 35 205 p+1.

Example 13

N-t-BOC-9,11-dibromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one (9,11-dibromo-t-BOC-cytisine)

To a 125 ml round bottom flask was added 2.24 gm (7.7 mmol) of t-BOC-cytisine in 65 ml 40 of methanol. The solution was treated with 1.32 gm (15.8 mmol) of sodium bicarbonate and

5 cooled to 0 ° C. A solution of bromine (0.810 ml, 15.8 mmol) in 25 ml of methylene chloride was added dropwise and the reaction mixture was stirred for 20 minutes. The reaction mixture was concentrated and partitioned between water and methylene chloride. The organic layer was washed with saturated aqueous sodium thiosulfate solution, brine and then dried. The solvent was evaporated in vacuo. The resulting foam (3.3 gm) was used directly in the next reaction without  
10 purification.  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  7.88 (s, 1H), 4.38, (br.s, 2H), 4.25 (d, 1H), 3.90 (dd, 1H), 3.45 (br.s, 1H), 3.00 (br. m, 2H), 2.45 (br.s, 1H), 2.00 (br.s, 2H), 1.29 (br.s, 9H) ppm; mass spectrum (thermospray) m/e 447, 449, 451 p+1, p+2, p+4.

Example 14

N-t-BOC-9,11-dimethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one (N-t-BOC-9,11-dimethylcytisine)

To a 5 ml Wheaton flask was added 0.139 gm (0.310 mmol) of the product of Example 13 and 1.5 ml of HMPA. The solution was treated with 0.060 gm (0.079 mmol) of *trans*-benzylchlorobis(triphenylphosphine)palladium and 0.413 ml (2.98 mmol) tetramethyltin. The reaction mixture was heated at 65°C for 12 hours. The dark reaction mixture was partitioned between 1:1 ethyl  
20 acetate : hexanes and 50 % brine. The organic phase was washed with brine and dried and the solvent was then evaporated. The residue was chromatographed on silica gel eluting first with ethyl acetate followed by 1% methanol in ethyl acetate. There was obtained 44mg (45%) of the title product which was used directly in the next step.  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  7.07 (s, 1H), 4.25 (d, 1H), 4.46 - 4.08 (m, 2H), 3.85 (dd, 1H), 3.05 (m, 3H), 2.40 (br.s, 1H), 2.10 (s, 6H), 1.97  
25 (br.s, 2H), 1.31 (br.s, 9H) ppm; mass spectrum (thermospray) m/e 319 p+1.

Example 15

9,11-Dimethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one hydrochloride salt (9,11-Dimethyl-cytisine, HCl salt)

The title product from Example 14 (0.044 gm; 0.138 mmol) in ethyl acetate was treated  
30 with an excess of 3 M HCl (g) in ethyl acetate. The reaction mixture was stirred for 1 hour and was partitioned between 2 N NaOH and methylene chloride. The organic layer was washed with brine, dried and the solvent evaporated. The residue was chromatographed on silica gel (elution with 2% methanol, 1 % NH<sub>4</sub>OH, 97% methylene chloride). The recovered desired product was then treated, in methanol-ether, with HCl gas. After filtration and 10 minutes drying in vacuo there  
35 was obtained 12 mg of the title product. An analytical sample was prepared by recrystallization from methanol : ether. mp > 270°C.

5

Example 16N-t-BOC-11-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one  
(11-vinyl-t-BOC cytisine)

To a 6 ml round bottom flask was added 0.066 gm (0.178 mmol) of 11-bromo-t-BOC-cytisine (prepared according to Example 1) and 1.5 ml of hexamethylphosphoramide (HMPA). The 10 solution was treated with 0.022 gm (0.03 mmol) of *trans*-benzylchlorobis(triphenylphosphine)palladium and 0.161 ml (0.55 mmol) tetravinyltin. The reaction mixture was heated at 65°C for 72 hours. The dark reaction mixture was partitioned between 1:1 ethyl acetate : hexanes and 50 % brine. The organic phase was washed with brine, dried and the solvent evaporated. The residue was chromatographed on silica gel eluting with 1% methanol in 15 methylene chloride. There was obtained 22 mg (40%) of the title product which was used directly in the next step.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 250 MHz)  $\delta$  7.58 (d, 1H), 6.71 (dd, 1H), 6.50 (d, 1H), 5.50 (d, 1H), 5.21 (d, 1H), 4.47 - 4.08 (m, 2H), 4.20 (d, 1H), 3.88 (dd, 1H), 3.38 (br.s, 1H), 3.00 (br. m, 2H), 2.41 (br.s, 1H), 1.98 (br.s, 2H), 1.25 (br.s, 9H) ppm; m/e 317 p+1.

20

11-Vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one  
hydrochloride salt (11-vinyl-cytisine, HCl salt)

The title product of Example 16 (0.022 gm; 0.069 mmol) in ethyl acetate was treated with an excess of 3 M HCl (g) in ethyl acetate. After 30 minutes a precipitate began to form. The reaction mixture was granulated for 24 hours to enhance the quality of the crystalline product. After 25 filtration and 10 minutes drying in vacuo there was obtained 0.014 gm of the title product. An analytical sample was prepared by recrystallization from methanol-ether. Mass spectrum (thermospray) m/e 217 p+1.

30

N-t-BOC-11-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one (N-t-BOC-11-ethyl-cytisine)

To a 4 ml round bottom flask was added 0.025 gm (0.079 mmol) of the title product of Example 16 in 1 ml of ethyl acetate. The solution was treated with 8 mg of palladium on barium sulfate catalyst and then placed under 1 atm. of hydrogen gas for 2 hours. The reaction mixture was filtered and concentrated to an oil. Chromatography on silica gel (1 % methanol in methylene chloride) afforded 21 mg (80 %) of the title product.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 250 MHz)  $\delta$  7.22 (d, 1H), 6.48 (d, 1H), 4.46 - 4.08 (m, 2H), 4.20 (d, 1H), 3.88 (dd, 1H), 3.23 (br.s, 1H), 3.00 (br.m, 2H), 2.45 (m, 3H), 2.00 (br.s, 2H), 1.26 (m, 12H) ppm ; mass spectrum (thermospray) m/e 319 p+1.

5

Example 1911-Ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one  
hydrochloride salt (11-Ethyl-cytisine, HCl salt)

The product of Example 18 (0.020 gm; 0.063 mmol) in ethyl acetate was treated with an excess of 3 M HCl(g) in ethyl acetate. After 30 minutes, a precipitate began to form. The reaction mixture was granulated for 24 hours to enhance the quality of the crystalline product. After filtration and 10 minutes drying in vacuo there was obtained 0.012 gm of the title product. An analytical sample was prepared by recrystallization from methanol-ether. Mass spectrum (thermospray) m/e 219 P+1.

15

Example 20N-t-BOC-11-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one  
(N-t-BOC-11-phenylcytisine)

To a 5 ml round bottom flask was added 0.076 gm (0.205mmol) of 11-bromo-t-BOC-cytisine (prepared according to the method of Example 1) and 1.0 ml of HMPA. The solution was treated with 0.025 gm (0.03 mmol) of *trans*-benzylchloro-bis(triphenylphosphine)palladium and 20 0.208 ml (0.64 mmol) tributylphenyltin. The reaction mixture was heated at 65°C for 48 hours. The dark reaction mixture was partitioned between 1:1 ethyl acetate : hexanes and 50 % brine. The organic phase was washed with brine, dried and the solvent evaporated. The residue was chromatographed on silica gel eluting with ethyl acetate. There was obtained 64mg (85%) of the title product which was used directly in the next step. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz) δ 7.38 (5H, m), 7.20 (d, 1H), 6.50 (d, 1H), 4.45 - 3.95 (m, 2H), 4.30 (d, 1H), 3.88 (dd, 1H), 3.06 (br.s, 1H), 3.02 - 25 2.58 (m, 2H), 2.39 (br.s, 1H), 1.90 (dd, 2H), 1.37 (s, 9H) ppm; mass spectrum (thermospray) m/e 367 p+1.

30

Example 2111-Phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one  
hydrochloride salt (N-t-BOC-11-phenylcytisine, HCl salt)

The product from Example 20 (0.064 gm; 0.174mmol) in ethyl acetate was treated with an excess of 3 M HCl(g) in ethyl acetate. After 30 minutes a precipitate began to form. The reaction mixture was granulated for 24 hours to enhance the quality of the crystalline product. After filtration and brief drying in vacuo there was obtained 0.043 gm of the title product. An analytical sample was prepared by recrystallization from methanol : ether. <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz) δ 7.38 35 (m, 5H), 7.20 (d, 1H), 6.50 (d, 1H), 4.1 (d, 1H), 3.95 (dd, 1H), 3.45 (br.s, 1H), 3.35 (d, 1H), 3.20 (dd, 1H), 2.95 (dd, 2H), 2.65 (br.s, 1H), 1.90 (dd, 2H) ppm; mass spectrum (thermospray) m/e 267 p+1.

5

Example 229-Bromo-3-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one  
(9-Bromo-3-methylcytisine)

To a 5 ml round bottom flask was added 0.035 gm (0.130mmol) 9-bromo cytisine (prepared previously) in 2 ml of acetone. To the resulting solution was added 0.0217 gm (0.258 mmol) potassium carbonate and 8.1  $\mu$ l (0.128 mmol) of methyl iodide. The reaction mixture was heated under reflux for 1.5 hours and then evaporated in vacuo. The residue was partitioned between methylene chloride and water. The organic phase was washed with brine, dried and the solvent evaporated. Chromatography on silica gel eluting with 1 % methanol in methylene chloride afforded 14 mg (38%) of the desired product.  $^1$ H NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  7.65 (d, 1H), 5.91 (d, 1H), 4.11 (d, 1H), 3.93 (dd, 1H), 2.87 (m, 3H), 2.43 (s, 1H), 2.25 (m, 2H), 2.13 (s, 3H), 1.80 (m, 2H) ppm; mass spectrum (particle beam) m/e 283, 285.

Example 233-Benzyl-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one (3-Benzyl-9-bromocytisine)

To a 10 ml round bottom flask was added 0.045 gm (0.167mmol) 9-bromocytisine (prepared according to the method of Example 2) in 2 ml of 1,2-dichloroethane. The above solution was treated with 0.0187 gm (0.184 mmol) benzaldehyde, 9.6  $\mu$ L acetic acid and 0.053 gm (0.25 mmol) sodium triacetoxyborohydride. The reaction mixture was stirred at room temperature for 2 hours and then partitioned between methylene chloride and 1 N HCl (aq). The organic phase was washed with brine, dried and the solvent evaporated in vacuo to a solid. Chromatography on silica gel eluting with 1 % methanol in methylene chloride afforded 16 mg (27%) of the title product.  $^1$ H NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  7.67 (d, 1H), 7.20 (m, 3H), 7.00 (m, 2H), 5.86 (d, 1H), 4.15 (d, 1H), 3.95 (dd, 1H), 3.43 (br.s, 2H), 2.93 (m, 2H), 2.85 (d, 1H), 2.45 (s, 1H), 2.35 (m, 2H), 1.85 (m, 2H) ppm; mass spectrum (particle beam) 359, 361.

30

Example 243-Benzyl-9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one (3-Benzyl-9-chloro-cytisine) and3-benzyl-11-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one  
(3-benzyl-11-chlorocytisine)

35 Preparation of N-benzylcytisine: To a 25 ml round bottom flask was added 0.510 gm (2.68 mmol) cytisine in 10 ml of 1,2-dichloroethane. The above solution was treated with 0.272 ml (2.68 mmol) benzaldehyde, 153  $\mu$ l acetic acid and 0.852 gm (4.02 mmol) sodium triacetoxyborohydride. The reaction mixture was stirred at room temperature for 2 hours and was then partitioned between methylene chloride and 1 N HCl (aq). The organic phase was washed with brine, dried and the solvent evaporated in vacuo to a solid. Chromatography on silica gel eluting with 1 %

5 methanol in methylene chloride afforded 434 mg (58%) of the title product which was used in the next step.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 250 MHz)  $\delta$  7.28 (dd, 1H), 7.15 (m, 3H), 6.98 (m, 2H), 6.52 (d, 1H), 5.92 (d, 1H), 4.10 (d, 1H), 3.88 (dd, 1H), 3.40 (dd, 2H), 2.88 (m, 3H), 2.39 (br.s, 1H), 2.32 (dd, 2H), 1.82 (dd, 2H) ppm.

To a 35 ml round bottom flask was added 0.434 gm (1.54 mmol) of N-benzylcytisine 10 above, in 17 ml of methylene chloride. To the above solution was added 0.207 gm (1.54 mmol) of N-chlorosuccinimide and the reaction mixture was heated under reflux for 16 hours. The reaction mixture was allowed to cool to room temperature and was then diluted with excess water. The organic phase was washed with brine, dried and the solvent evaporated in vacuo. The residue was flash chromatographed on silica gel eluting with methylene chloride : methanol (99.5: 0.5). 15 Two products were obtained. The least polar material (the first to elute) was identified as 9-chloro-N-benzylcytisine 40 mg  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 250 MHz)  $\delta$  7.49 (d, 1H), 7.22 (m, 3H), 7.00 (m, 2H), 5.89 (d, 1H), 4.16 (d, 1H), 3.94 (dd, 1H), 3.42 (dd, 2H), 2.90 (m, 3H), 2.45 (br.s, 1H), 2.35 (dd, 2H), 1.87 (dd, 2H) ppm; mass spectrum (thermospray) m/e 315 p+1.

The more polar, second material to elute, was 11-chloro-N-benzyl-cytisine 250 mg;  $^1\text{H}$  20 NMR ( $\text{CDCl}_3$ , 250 MHz)  $\delta$  7.32 (d, 1H), 7.19 (m, 3H), 6.98 (m, 2H), 6.51 (d, 1H), 4.05 (d, 1H), 3.88 (dd, 1H), 3.45 (br.s, 3H), 3.02 (d, 1H), 2.90 (d, 1H), 2.41 (br.s, 1H), 2.30 (dd, 2H), 1.88 (br.s, 2H) ppm.

#### Preparation of 9-iodo-t-boc-cytisine

To a solution of 1.06 gm (3.6 mmol) t-boc cytisine in 50 ml of methanol was added 548 mg 25 (5.5 mmol) calcium carbonate followed by the dropwise addition (over 20 min) of a solution of iodine monochloride as a 1M solution in dichloromethane (5.5 ml, 5.5 mmol). The mixture was stirred for 5 hours at room temperature and then was quenched with a mixture of aqueous thiosulfate and bicarbonate. Ethyl acetate was added to the mixture and the organic phase was separated, washed with brine and then dried and evaporated. The residue was chromatographed 30 on silica gel, eluting with ethyl acetate hexane (7:3). There was obtained 737 mg (48 %) of the desired iodo-t-boc cytisine.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7.89 (d,  $J$  = 7.5 Hz, 1H), 5.88 (br.s, 1H), 4.23 (d,  $J$  = 15.6 Hz, 1H), 4.36 - 4.08 (br.m, 2H), 3.85 (dd,  $J$  = 15.1 Hz,  $J$  = 6.0 Hz, 1H), 3.00 (br.m, 3H) 2.40 (br.s, 1H), 1.95 (br.s, 2H), 1.31 (br.s, 9H) ppm; mass spectrum (thermospray) m/e 417 p+1.

#### 35 Preparation of 9-morpholinocytisine

To a flame dried flask with condenser and magnetic stirrer under argon was placed 100 mg (0.27 mmole) 9-bromo-tboc-cytisine and 5 ml toluene. The flask was evacuated and then placed under argon gas. The solution was treated with 0.027 ml (0.31 mmole) morpholine, 35 mg (0.36 mmole) sodium tert-butoxide and 12 mg (0.019 mmole) 2,2'-bis(diphenylphosphino)-1,1'-40 binaphthyl (BINAP). The mixture was evacuated briefly using a standard vacuum source and then

5 placed once again under argon. The catalyst, bis[1,2-bis(diphenylphosphino)ethane] palladium(0) (dppe<sub>2</sub>-Pd), 10 mg ( 0.01 mmole) was added and the reaction mixture was once again briefly placed under vacuum and then brought to atmospheric pressure under argon. The reaction mixture was heated to 130° C for 30 min. Monitoring of the reaction progress could be accomplished by thin layer chromatography (tlc). The solvent was then concentrated in vacuo and

10 the residue was chromatographed directly on silica gel using ethyl acetate hexane (8/2). 9-morpholino-t-boc cytisine, was obtained as an oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  6.63 (br.s, 1H), 5.99 (br.s, 1H), 4.31 - 4.00 (m, 2 H), 4.16 (d, 1H), 3.83 (br.m, 5 H), 3.23 (m, 2 H), 3.04 - 2.91 (br. m, 5 H), 2.35 (br.s, 1H), 1.90 (m, 2 H), 1.27 (br.s, 9H) ppm. mass spectrum (thermospray) m/e 376 p+1.

15 Removal of the t-boc protecting group was accomplished with overnight stirring at room temperature with anhydrous 3 M HCl in ethyl acetate to afford 13 mg (14 %) of 9-morpholino-cytisine hydrochloride; Mass spectrum (thermospray) m/e 276 p+1.

The following derivatives were prepared through this procedure:

20 9-benzylamino-t-boc-cytisine: (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.30 (m, 5H), 6.19 (br.s, 1H), 5.96 (br.s, 1H), 4.34 - 3.99 (m, 5H), 3.86 (m, 1H), 2.91 (m, 3H), 2.36 (br.s, 1H), 1.90 (m, 2 H), 1.31 (br.s, 9H) ppm; Mass spectrum (thermospray) m/e 396 p+1.

25 9-benzylamino-cytisine hydrochloride: <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.48 (m, 2H), 7.40 (m, 3H), 7.27 (d, J = 7.5 Hz, 1H), 6.37 (d, J = 7.6 Hz, 1H), 4.47 (ABq, J = 13.3 Hz, 2H), 4.27 (d, J = 15.8 Hz, 1H), 4.09 (m, 1H), 3.42 (m, 6H), 2.79 (br.s, 1H), 2.12 (ABq, J = 13.8 Hz, 2H) ppm; Mass spectrum (thermospray) m/e 296 p+1.

30 9-pyrrolidino-tboc-cytisine: (CDCl<sub>3</sub>, 400 MHz)  $\delta$  6.33 (br.s, 1H), 5.94 (br.s, 1H), 4.33 - 4.02 (br. m, 2H), 4.16 (m, 1H), 3.79 (dd, J = 15.4 Hz, J = 6.4 Hz, 1 H), 3.46 (br.s, 2 H), 3.14 - 2.91 (br.m, 4H), 2.35 (br.s, 1H), 1.89 (br.m, 5 H), 1.31 (br.s, 9H) ppm; Mass spectrum (thermospray) m/e 360 p+1.

35 9-pyrrolidino-cytisine: Mass spectrum (thermospray) m/e 260 p+1.

9-dimethylamino-tboc-cytisine: (CDCl<sub>3</sub>, 400 MHz)  $\delta$  6.6 - 6.4 (br.m, 1H), 5.99 (m, 1H), 4.37 - 4.02 (br.m, 2H), 4.18 (br.d, 1H), 3.80 (dd, J = 15.1 Hz, J = 6.0 Hz, 1H), 3.06 - 2.92 (br.m, 3H), 2.75 (s, 6H), 2.36 (br.m, 1H), 1.91 (br.m, 3H), 1.29 (br.s, 9H) ppm; Mass spectrum (thermospray) m/e 334 p+1.

40 9-dimethylamino-cytisine: (CDCl<sub>3</sub>, 400 MHz)  $\delta$  6.61 (d, J = 7.5 Hz, 1 H), 5.92 (d, J = 7.5 Hz, 1 H), 4.14 (d, J = 15.6 Hz, 1H), 3.89 (dd, J = 15.6 Hz, J = 6.6 Hz, 1H), 3.0 (br.m, 4 H), 2.78 (br.s, 6H), 2.28 (br.s, 1H), 1.92 (s, 3H) ppm; Mass spectrum (thermospray) m/e 234 p+1.

HRMS (FAB) calc'd for C<sub>13</sub>H<sub>19</sub>N<sub>3</sub>O +H 234.1606

found 234.1613

## 5 Preparation of 9-acetyl-cytisine

To a flame dried flask with condenser and magnetic stirrer under argon was placed 100 mg (0.27 mmole) 9-bromo-tboc-cytisine and 4 ml DMF. The flask was evacuated and then placed under argon gas. The solution was treated with 0.045 ml (0.32 mmole) triethylamine, 0.175 ml (1.35 mmole) of butylvinylether, 4.2 mg (0.0076 mmole) diphenylphosphinoferrocene (dppf), and 10 1.5 mg (0.00075 mmole) palladium acetate. The mixture was evacuated briefly with a vacuum source and then placed once again under 1 atm argon. The reaction mixture was heated to 100°C for 1 hr whereupon the mixture turned black. TLC analysis (9/1 ethyl acetate/hexane) indicated the reaction was not complete and 15 mg (0.067 mmole) palladium acetate and 42 mg (0.076 mmole) of dppf was added. The mixture was evacuated briefly with a vacuum source and then 15 placed once again under argon. Heating was reinitiated at 100°C for 0.5 hr and then the reaction mixture was allowed to cool to room temperature. The mixture was poured into 50 % saturated brine solution and extracted with 1/1 ethylacetate / hexane. The extract was washed with brine and then dried and evaporated to afford 90 mg of a crude oil. Chromatography on silica gel with 9/1 ethylacetate / hexane provided 45 mg (71%) of the desired 9-acetyl-t-boc-cytisine. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  8.08 (d, J = 7.5 Hz, 1H), 6.17 (br.s, 1H), 4.21 (d, J = 15.8 Hz, 1H), 4.36 - 4.09 (br.m, 2H), 3.82 (dd, J = 15.8 Hz, J = 6.2 Hz, 1H), 3.04 (br.s, 3H), 2.63 (s, 3H), 2.45 (br.s, 1H), 1.96 (q, J = 14.7 Hz, 2H), 1.3 (br.s, 9H) ppm; Mass spectrum (thermospray) m/e 333 p+1. Removal of the t-boc protecting group was accomplished with overnight stirring at room temperature with anhydrous 3 M HCl in ethyl acetate to afford a brown powder. This hydrochloride salt was 20 converted to the free base by treatment with 25% NaOH solution and extraction with methylene chloride. After treatment with activated charcoal and filtration, the residue after evaporation of the organic phase was chromatographed on silica gel eluting with 97:2:1 methylene chloride: methanol: ammonium hydroxide to afford the desired 9-acetyl-cytisine as the free base. The material was converted to the hydrochloride salt using anhydrous 3 M HCl in ethyl acetate (12.6 25 mg 20%). <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz)  $\delta$  8.03 (d, J = 7.7 Hz, 1H), 6.44 (d, J = 7.7 Hz, 1H), 4.12 (d, J = 16.0 Hz, 1H), 3.87 (dd, J = 15.8 Hz, J = 6.44 Hz, 1H), 3.40 (br.m, 5H), 2.72 (br.s, 1H), 2.40 (s, 3H), 1.97 (q, J = 13.7 Hz, 2H) ppm; <sup>13</sup>C NMR (free base, CDCl<sub>3</sub>, 100 MHz)  $\delta$  198.0, 162.0, 158.0, 142.2, 123.0, 105.0, 53.4, 52.9, 50.2, 36.2, 31.1, 27.8, 25.9 ppm; Mass spectrum (thermospray) m/e 233 p+1;

30 35 HRMS (FAB) calc'd for C<sub>13</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub> +H 233.1290  
found 233.1286

## Preparation of 9-(2-tetrahydrofuryl)-cytisine

To a flame dried flask with condenser and magnetic stirrer under argon was placed 300 mg (0.81 mmole) 9-bromo-tboc-cytisine, 0.061 ml (0.81 mmole) of 23, dihydrofuran and 10 ml 40 DMF. The solution was treated with 230 mg (2.4 mmole) of potassium acetate, 225 mg (0.81

5 mmole) tetra-n-butylammonium acetate, 5.2 mg (0.02 mmole) triphenylphosphine and 4.5 mg (0.02 mmole) of palladium acetate. The mixture was heated to 90°C for 16 hrs under nitrogen. The reaction mixture was allowed to cool to room temperature and was then partitioned between 50 % brine solution and 1/1 ethyl acetate / hexane. The organic phase was washed once again with saturated brine and then dried and evaporated in vacuo. The resulting crude 9-(2-[2,3-dihydrofuran])-t-boc-cytisine was hydrogenated in 3 ml of ethanol with 10% palladium on carbon under 45 psi hydrogen gas for 5 min. The catalyst was removed and the filtrate was evaporated in vacuo to afford crude 9-(2-tetrahydrofuran)-t-boc-cytisine. The protecting group was removed by heating with 0.020 ml trifluoroacetic acid in dichloroethane for 10 min. The reaction mixture was added to water and the solution was made basic with sodium hydroxide solution. The aqueous phase was extracted with methylene chloride and the organic phase was dried and evaporated in vacuo.  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.38 (d, J = 7.1 Hz, 1H), 6.00 (m, 1H), 5.00 (m, 1H), 4.10 (dd, J = 15.6 Hz, J = 5.8 Hz, 1H), 4.02 (m, 1H), 3.87 (m, 2H), 2.98 (br.m, 4H), 2.86 (br.s, 1H), 2.42 (m, 1H), 2.29 (br.s, 1H), 1.92 (br.s, 4H), 1.70 (m, 2H) ppm; mass spectrum (thermospray) m/e 261 p+1. The residue (30 mg) was converted to the HCl salt (34 mg 14 %) by treatment with anhydrous 3M HCl in ethyl acetate. Mass spectrum (thermospray) m/e 261 p+1.

#### Preparation of 9-cyanocytisine

To a flame dried flask with condenser and magnetic stirrer under argon was placed 300 mg (0.81 mmole) 9-bromo-tboc-cytisine, 124 mg (1.05 mmole) of zinc cyanide and 470 mg (0.41 mmole) of tetrakis(triphenylphosphine) palladium in 10 ml DMF. The reaction mixture was heated to 80°C for 16 hrs and then allowed to cool to room temperature. The reaction mixture was filtered and then partitioned between 50 % saturated bicarbonate solution and extracted with methylene chloride. The organic phase was washed with brine dried and evaporated in vacuo. 9-cyano-t-boc-cytisine:  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.70 (br.s, 1H), 6.15 (br.s, 1H), 4.18 (br.m, 3H), 3.86 (br.m, 1H), 3.08 (br.m, 3H), 2.45 (br.s, 1H), 1.99 (br.s, 2H), 1.31 (br.s, 9H) ppm; Mass spectrum (thermospray) m/e 316 p+1. The protecting group was removed by heating with 10 equivalents of trifluoroacetic acid in dichloroethane for 1 hr. The mixture was cooled to room temperature and then partitioned between water and methylene chloride. The aqueous phase was made basic to pH - 12 with sodium hydroxide. The organic phase was separated and washed with saturated brine solution and dried and evaporated. 9-cyanocytisine was converted to the hydrochloride salt by treatment with anhydrous 3M HCl in ethylacetate 102 mg (51 %)  $^1\text{H}$  NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  8.02 (d, J = 7.5 Hz, 1H), 6.51 (d, J = 7.6 Hz, 1H), 4.24 (d, J = 16.2 Hz, 1H), 4.03 (dd, J = 16.2 Hz, J = 6.6 Hz, 1H), 3.48 (br.m, 5H), 2.80 (br.s, 1H), 2.12 (q, J = 13.5 Hz, 2 H) ppm; IR (film)  $\lambda$  2221, 1642, 1555 cm<sup>-1</sup>; Mass spectrum (thermospray) m/e 216 p+1.

HRMS (FAB) calc'd for C<sub>12</sub>H<sub>13</sub>N<sub>3</sub>O +H 216.1137

5 found 216.1134

Preparation of 9-(2-propenyl)cytisine, 9-(2-propyl)cytisine and 9-acetylcytisine  
2-propenylboronic acid

To a solution of 2-bromopropene (2.6 ml, 0.031 mol) in 50 ml anhydrous THF at - 78° C was added 12.6 ml (0.032 mol) n-butyl lithium in hexanes dropwise (0.5 ml min). The reaction 10 mixture was stirred at -78°C for 0.5 hours and then treated with 10.5 ml (0.045 mole) triisopropylborate over 5 minutes. The reaction mixture was stirred for 2 hours and then warmed slowly to room temperature. The reaction was quenched with 2N HCl until pH = 1 and concentrated to 1/2 volume before diluting with ethyl acetate. The organic phase was extracted with 1N NaOH three times and then the pH was adjusted to 1.0 with conc HCl at 0°C. The 15 aqueous layer was extracted with ethyl acetate, washed with brine dried and evaporated in vacuo to afford 0.88 gm (33%). The crude product was used directly in the next step. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  6.11 (br.s, 1H), 5.83 (br.s, 1H), 1.88 (s, 3H) ppm.

9-(2-propenyl)-tboC-cytisine

A mixture of 9-bromo-tboC-cytisine 1.0 gm (0.0027mol) and 1.2 gm (0.014 mol) 2-propenylboronic acid was dissolved in 86.0 ml ethanol-water (9:1) together with 0.94 gm (0.0089 mol) sodium carbonate and 0.1 gm (0.086 mmol) tetrakis(triphenyl-phosphine)palladium. The reaction mixture was heated under reflux and under argon gas for 18 hours. After cooling to room temperature, the reaction mixture was filtered and concentrated. The residue was redissolved in ethyl acetate and washed with water and then brine. The crude material, obtained by evaporation, 25 was pad-chromatographed on silica gel using a gradient solvent system for elution. Thus the column was flushed with 50% ethyl acetate / hexane followed by 80 % ethyl acetate / hexane and finally 1 % methanol ethyl acetate to afford 9-(2-propenyl)-tboC-cytisine after concentration and drying in vacuo. (0.93 gm, quant). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.26 (m, 1H), 6.04 (br.s, 1H), 5.61 (s, 1H), 5.12 (s, 1H), 4.37 - 4.06 (br.m, 2H), 4.19 (d, J = 15.6Hz, 1H), 3.81 (dd, J = 15.6 Hz, J = 6.4 Hz, 1H), 2.98 (br.m, 3H), 2.39 (br.s, 1H), 2.05 (s, 3H), 1.92 (m, 2H), 1.29 (br.s, 9H) ppm; mass spectrum (thermospray) m/e 331 p+1. The protecting group was removed by treatment with 5 ml trifluoroacetic acid in 100 ml dichloroethane under reflux for 45 min. The reaction mixture was cooled to room temperature and was then washed with 2N sodium hydroxide solution followed by brine. The organic layer was dried over sodium sulfate and evaporated to furnish 9-(2-propenyl)cytisine <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.29 (d, J = 7.3 Hz, 1H), 5.99 (d, J = 7.3 Hz, 1H), 5.71 (t, J = 1Hz, 1H), 5.17 (t, J = 1Hz, 1H), 4.15 (d, J = 15.6Hz, 1H), 3.88 (dd, J = 15.6 Hz, J = 6.5 Hz, 1H), 3.14 - 2.99 (br.m, 4H), 2.90 (br.s, 1H), 2.34 (br.s, 1H), 2.10 (s, 3H), 1.94 (br.s, 2H) ppm; Mass spectrum (thermospray) m/e 231 p+1.

HRMS (FAB) calc'd for C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O +H 231.1497

5        found 231.1483

9-acetyl-tboc-cytisine

9-(2-propenyl)-tboc-cytisine from above (501 mg, 1.5 mmol) in 45 ml of dioxane was treated with 1.9 gm (0.19 mmol) osmium tetroxide (2.5 % sol in t-butanol) and stirred at room temperature for 4 hours. The green reaction mixture was treated with water (5 ml) and 350 mg (3 mmol) of n-methylmorpholine N-oxide. After 0.5 hours, the solution was treated with 680 mg (3.2 mmol) sodium periodate and the reaction mixture was stirred overnight. The color of the mixture was now light yellow and a precipitate had been formed. The reaction mixture was treated with water and 2 ml 2N HCl and extracted with ethyl acetate. The organic phase was washed with brine and then dried and evaporated. The residue was passed through a pad of silica gel eluting with 1 % methanol / ethyl acetate to afford after evaporation 433 mg (86 %) of acetyl-t-boc-cytisine as a solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  8.08 (d,  $J$  = 7.5 Hz, 1H), 6.17 (br.s, 1H), 4.21 (d,  $J$  = 15.8 Hz, 1H), 4.36 - 4.09 (br.m, 2H), 3.82 (dd,  $J$  = 15.8 Hz,  $J$  = 6.2 Hz, 1H), 3.04 (br.s, 3H), 2.63 (s, 3H), 2.45 (br.s, 1H), 1.96 (q,  $J$  = 14.7 Hz, 2H), 1.3 (br.s, 9H) ppm; mass spectrum (thermospray) m/e 333 p+1.

20      9-(2-propyl)cytisine

9-(2-propenyl)-tboc-cytisine (418 mg, 1.2 mmol) in 40 ml methanol was treated with 209 mg of 10 % palladium on carbon. The mixture was placed under 35 psi hydrogen pressure for 7 hours in a Parr shaker. The reaction mixture was then filtered and evaporated in vacuo. The residue was partitioned between ethyl acetate and brine. The organic phase was dried and evaporated to afford 305 mg (73 %) of the desired product. NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7.11 (d,  $J$  = 7.1 Hz, 1H), 6.03 (br.s, 1H), 4.18 (d,  $J$  = 15.6 Hz, 1H), 4.37 - 4.06 (br.m, 2H), 3.81 (dd,  $J$  = 15.5 Hz,  $J$  = 6.6 Hz, 1H), 3.20 - 2.80 (br.m, 4H), 2.38 (br.s, 1H), 1.93 (q,  $J$  = 12.9 Hz, 2H), 1.30 (br.s, 9H), 1.13 (obsc.d, 6H) ppm; mass spectrum (thermospray) m/e 333 p+1. The protecting group was removed by treatment with 5 ml trifluoroacetic acid in 100 ml dichloroethane under reflux for 45 min. The reaction mixture was cooled to room temperature and was then washed with 2N sodium hydroxide solution followed by brine. The organic layer was dried over sodium sulfate and evaporated: The hydrochloride salt was prepared by treatment of the residue with anhydrous 3N HCl in ethyl acetate to furnish 9-(2-propyl)cytisine  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 400 MHz)  $\delta$  7.34 (d,  $J$  = 7.3 Hz, 1H), 6.33 (d,  $J$  = 7.3 Hz, 1H), 4.02 (d,  $J$  = 15.2 Hz, 1H), 3.83 (dd,  $J$  = 15.8 Hz,  $J$  = 6.6 Hz, 1H), 3.23 (br.m, 5H), 2.88 (spt, 1H), 2.64 (br.s, 1H), 1.93 (q,  $J$  = 13.7 Hz, 2H), 0.96 (d,  $J$  = 7.0 Hz, 6H) ppm; mass spectrum (thermospray) m/e 233 p+1.

HRMS (FAB) calc'd for  $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O} + \text{H}$  233.1654

found 233.1658

9-Carbomethoxycytisine

5        A mixture of 600 mg (1.62 mmol) 9-bromo-N-tboc-cytisine in 40 ml of methanol was  
treated with 10 mg (0.04 mmol) palladium acetate, 20 mg (0.05 mmol) 1,3-  
diphenylphosphinylpropane (dppp) and 917 mg (9.2 mmol) potassium bicarbonate. The reaction  
mixture was placed in a Parr apparatus and then degassed using vacuum. The container was  
then placed under 16 psi carbon monoxide pressure and slowly heated to 70°C. The reaction was  
10      agitated for 16 hours while the pressure rose to 36 psi. The reaction mixture was cooled, purged  
with a nitrogen atmosphere and then filtered. The filtrate was evaporated. The residue was  
partitioned between ethyl acetate and water, and the organic phase was washed with brine dried  
and evaporated. There was obtained 485 mg (86 %) of 9-carbomethoxy-N-tboc-cytisine. <sup>1</sup>H NMR  
(CDCl<sub>3</sub>, 400 MHz)  $\delta$  8.12 (d, J = 7.3Hz, 1H), 6.12 (d, J = 7.5Hz, 1H), 4.18 (d, J = 16Hz, 1H), 4.4 -  
15      4.1 (br.m, 2H), 3.85 (obsc, 1H), 3.87 (s, 3H), 3.05 (br.s, 3H), 2.45 (br.s, 1H), 1.95 (obsc.q, 2H),  
1.31 (br.s, 9H) ppm; mass spectrum (thermospray) m/e 349 p+1. The protecting group was  
removed by treatment of 67 mg of the ester with 0.5 ml trifluoroacetic acid in 10 ml dichloroethane  
under reflux for 20 minutes. The reaction mixture was cooled to room temperature and treated  
with aq hydroxide solution and methylene chloride. The organic phase was washed with brine and  
20      then dried and evaporated in vacuo. The residue was dissolved in ethyl acetate and treated with  
anhydrous 3M HCl in ethyl acetate to afford 9-carbomethoxycytisine hydrochloride (11 mg). <sup>1</sup>H  
NMR (D<sub>2</sub>O, 400 MHz)  $\delta$  8.11 (d, J = 7.7 Hz, 1H), 6.43 (d, J = 7.7 Hz, 1H), 4.12 (d, J = 16 Hz, 1H),  
3.87 (dd, J = 16 Hz, J Hz, 1H), 3.67 (s, 3H), 3.40 (br.m, 5H), 2.70 (br.s, 1H), 1.96 (q, J = Hz, 2H)  
ppm; mass spectrum (thermospray) m/e 249 p+1;

25      HRMS (FAB) calc'd for C<sub>13</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub> +H 249.1239  
found 249.1231

Preparation of N-t-boc-9-cytisinecarboxaldehyde

30      A solution of 527 mg (1.5 mmol) 9-carbomethoxy-N-tboc-cytisine in 40 ml of methylene  
chloride at -78°C was treated with 1.67 ml (1.67 mmol) of a 1M solution of DIBAL-H in methylene  
chloride and stirred for 3 hours at low temperature. The reaction mixture was quenched with 2 N  
HCl and warmed to 0°C. The organic phase was washed with brine dried and evaporated. The  
residue was chromatographed on silica gel using a gradient elution consisting of 1.5 - 3 % MeOH  
in ethyl acetate to afford 292 mg (60 %) of the desired aldehyde.

35      HRMS (FAB) calc'd for C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> +H 219.1134  
found 219.1123

Preparation of 9-(2-methoxyphenyl)cytisine

40      A solution of 9-bromo-tboc-cytisine [251 mg (0.68 mmol)] and 114 mg (0.75 mmol) o-  
methoxyphenylboronic acid in 18 ml ethanol-water (9:1) was treated with 186 mg (1.7 mmol)  
sodium carbonate and then placed under vacuum. The evacuated flask was brought to 1 atm with  
argon and then treated with 17 mg (0.015 mmol) tetrakis (triphenylphosphine)palladium (0). The

5 flask was evacuated briefly and then placed under 1 atm argon and heated under reflux for 6 hours. The dark reaction mixture was allowed to cool to room temperature before filtering of the solid mass. The filtrate was extracted with ethyl acetate and the organic layer was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was chromatographed on a silica pad eluting first with 8:2 ethyl acetate hexane followed by 1% methanol in ethyl acetate.

10 The product 9-(2-methoxyphenyl)-t-boc-cytisine (250 mg, 93 %) was obtained as a white solid. The protecting group was removed by treatment with anhydrous 3M HCl in ethyl acetate at room temperature followed by recrystallization from methanol ether to afford 204 mg (98%) of the hydrochloride salt.

HRMS (FAB) calc'd for  $C_{18}H_{20}N_2O_2 + H$  297.1603

15 found 297.1584

Preparation of 9-(2,6-difluorophenyl)cytisine

A solution of 9-bromo-tboc-cytisine [740 mg (2.0 mmol)] and 1.2 ml (5.2 mmol) triisopropylborate in 50 ml THF was cooled to - 78°C before dropwise addition of 0.85 ml (2.1 mmol) of 2.5 M n-butyl lithium. The reaction mixture was stirred at - 78°C for 3 hours and 2 hours 20 at 0°C before quenching with 2N HCl. Most of the THF was evaporated and the residuals were extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and evaporated in vacuo. The resulting solid was triturated with a minimum amount of ether to afford 590 mg (88 %) of N-tboc-cytisine-9-boronic acid product as a mixture of boronic acid and anhydrides mass spectrum (thermospray) m/e 335 p+1

25 A mixture of N-tboc-cytisine-9-boronic acid [100 mg (0.3 mmol)] and 57.6 mg (0.3 mmol) 2,6-difluoro-1-bromobenzene was prepared in 10 ml ethanol-water (9:1) containing 140 mg (1.3 mmol) of sodium carbonate. The flask was evacuated briefly and then placed under 1 atm argon. The mixture was treated with 14 mg (0.012 mmol) tetrakis (triphenylphosphine)palladium (0), briefly evacuated and then was placed under 1 atm argon and heated to reflux for 16 hours. The 30 reaction mixture was filtered and evaporated in vacuo. The residue was taken up in ethyl acetate and water and the organic phase was washed with brine, dried and evaporated. The crude product was pad chromatographed on silica eluting first with 8:2 ethyl acetate hexane followed by 1% methanol in ethyl acetate. This afforded 51 mg (40 %) of 9-(2,6-difluorophenyl)-N-t-boc-cytisine. The protecting group was removed by treatment with 0.1 ml trifluoroacetic acid in 5 ml 35 methylene chloride under reflux for 3 hours. The reaction mixture was cooled to room temperature and treated with aq sodium bicarbonate solution. The organic phase was washed with brine and then dried and evaporated in vacuo. The residue was dissolved in ethyl acetate and treated with anhydrous 3M HCl in ethyl acetate to afford 9-(2,6-difluorophenyl)cytisine hydrochloride (21 mg). mass spectrum (thermospray) m/e 303 p+1

5 The following compounds were prepared as described above:  
9-[2-(1,1,1-trifluoromethylpropenyl)cytisine HRMS (FAB) calc'd for  $C_{14}H_{15}F_3N_2O +H$  285.1215  
found 285.1203  
9-(4-methoxyphenyl)cytisine mass spectrum (thermospray) m/e 297 p+1

10 9-(2-ethoxy-5-methylphenyl)cytisine HRMS (FAB) calc'd for  $C_{20}H_{24}N_2O_2 +H$  325.1916  
found 325.1897  
9-(2-benzofuranyl)cytisine HRMS (FAB) calc'd for  $C_{19}H_{18}N_2O_2 +H$  307.1  
found 307.1451  
9-(2-thienyl)cytisine HRMS (FAB) calc'd for  $C_{15}H_{16}N_2OS +H$  273.1062  
15 found 273.1055  
9-(3-thienyl)cytisine HRMS (FAB) calc'd for  $C_{15}H_{16}N_2OS+H$  273.1062  
found 273.1036  
9-[3-(4-methylthienyl)]cytisine HRMS (FAB) calc'd for  $C_{16}H_{18}N_2OS +H$  287.1218  
found 287.1213

20 9-[2-(3-methylthienyl)]cytisine HRMS (FAB) calc'd for  $C_{16}H_{18}N_2OS +H$  287.1218  
found 287.1223  
9-[3-(2-fluoropyridyl)]cytisine HRMS (FAB) calc'd for  $C_{16}H_{16}FN_3O +H$  286.1356  
found 286.1338  
9-(2-pyridyl)cytisine mass spectrum (thermospray) m/e 268 p+1

25 9-(2-furanyl)cytisine HRMS (FAB) calc'd for  $C_{15}H_{16}N_2O_2 +H$  257.1290  
found 257.1305  
9-(3-furanyl)cytisine HRMS (FAB) calc'd for  $C_{15}H_{16}N_2O_2 +H$  257.1290  
found 257.1299  
9-(2-trifluoromethylphenyl)cytisine mass spectrum (thermospray) m/e 335 p+1

30 9-(4-trifluoromethylphenyl)cytisine HRMS (FAB) calc'd for  $C_{18}H_{17}F_3N_2O +H$  335.1371  
found 335.1367  
9-phenylcytisine mass spectrum (thermospray) m/e 267 p+1  
11-phenylcytisine mass spectrum (thermospray) m/e 267 p+1  
9-(2-methylphenyl)cytisine HRMS (FAB) calc'd for  $C_{18}H_{20}N_2O +H$  281.1654  
35 found 281.1632  
9-(3-acetylphenyl)cytisine HRMS (FAB) calc'd for  $C_{19}H_{20}N_2O_2 +H$  309.1603  
found 309.1617  
9-(2-chlorophenyl)cytisine HRMS (FAB) calc'd for  $C_{17}H_{17}ClN_2O +H$  301.1108  
found 301.1114

5        9-(3,4-dichlorophenyl)cytisine HRMS (FAB) calc'd for C<sub>17</sub>H<sub>16</sub>Cl<sub>2</sub>N<sub>2</sub>O +H 335.0718  
          found 335.0692

      9-(2-fluorophenyl)cytisine HRMS (FAB) calc'd for C<sub>17</sub>H<sub>17</sub>FN<sub>2</sub>O +H 285.1403  
          found 285.1379

      9-(4-fluorophenyl)cytisine HRMS (FAB) calc'd for C<sub>17</sub>H<sub>17</sub>FN<sub>2</sub>O +H 285.1403  
10      found 285.1397

      9-(3-fluorophenyl)cytisine HRMS (FAB) calc'd for C<sub>17</sub>H<sub>17</sub>FN<sub>2</sub>O +H 285.1403  
          found 285.1401

      9-(3,5-difluorophenyl)cytisine HRMS (FAB) calc'd for C<sub>17</sub>H<sub>16</sub>F<sub>2</sub>N<sub>2</sub>O +H 303.1309  
          found 303.1295

15      9-(2,4-difluorophenyl)cytisine HRMS (FAB) calc'd for C<sub>17</sub>H<sub>16</sub>F<sub>2</sub>N<sub>2</sub>O +H 303.1309  
          found 303.1297

      9-(2-fluoro-4-chlorophenyl)cytisine HRMS (FAB) calc'd for C<sub>17</sub>H<sub>16</sub>FCIN<sub>2</sub>O +H 319.1013  
          found 319.1009

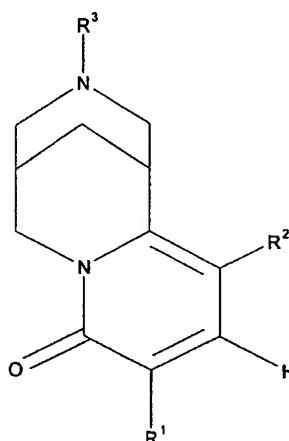
      9-(2-fluoro-4-methoxyphenyl)cytisine mass spectrum (thermospray) m/e 315 p+1  
20      9-(2,5-difluorophenyl)cytisine HRMS (FAB) calc'd for C<sub>17</sub>H<sub>16</sub>F<sub>2</sub>N<sub>2</sub>O +H 303.1309  
          found 303.1335

      9-(2-thiazoyl)cytisine mass spectrum (thermospray) m/e 274 p+1

5

CLAIMS

1. A pyridone-fused azabicyclic compound of the formula



its enantiomers, diastereomers and stereoisomers, and their pharmaceutically acceptable salts and prodrugs,

10 wherein R<sup>1</sup> and R<sup>2</sup> are each independently selected from

a) H, halo, CF<sub>3</sub>, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, CH<sub>2</sub>OH, -C(O)R wherein R is H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl and benzyl including substituted alkyl, aryl and benzyl, cyano, C≡CR, wherein R is H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl including substituted alkyl, aryl, -S(O)<sub>n</sub>R, wherein R is H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl including substituted alkyl, aryl and n is 0,1,2, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkenyl, amino, di-[(C<sub>1</sub>-C<sub>6</sub>)alkyl]amino, (C<sub>1</sub>-C<sub>6</sub>)monoalkylamino, (C<sub>6</sub>-C<sub>10</sub>)aryl amino, (C<sub>3</sub>-C<sub>8</sub>)cycloalkylamino, heteroaryl amino, cycloheteroalkylamino and CON(R<sup>5</sup>)<sub>2</sub> wherein each R<sup>5</sup> is selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl and (C<sub>6</sub>-C<sub>10</sub>)aryl; and

b) CO<sub>2</sub>R wherein R is selected from H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, phenyl and benzyl; and

c) optionally benzene-fused (C<sub>6</sub>-C<sub>10</sub>)aryl, optionally benzene-fused (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, optionally benzene-fused heteroaryl and optionally benzene-fused cycloheteroalkyl, wherein said heteroaryl group contains five to ten atoms comprising one to four heteroatoms, said cycloheteroalkyl contains 4 to 8 atoms comprising one or two heteroatoms selected from N, S and O;

and wherein any of the alkyl, alkenyl, aryl, cycloalkyl, cycloheteroalkyl and heteroaryl groups in a), b) and c) are optionally substituted with one or more substituents selected from halogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, hydroxy, hydroxymethyl, CHO and CO<sub>2</sub>R wherein R is as described above; and

R<sup>3</sup> is selected from H, optionally substituted benzyl and methyl;

with the provisos that R<sup>1</sup> and R<sup>2</sup> are not both hydrogen and when R<sup>3</sup> is H, then R<sup>1</sup> and R<sup>2</sup> when selected from H, Br and Cl, cannot be the same.

5        2.        The compound according to claim 1 wherein aryl is optionally substituted phenyl or naphthyl, cycloalkyl is optionally substituted and optionally unsaturated cyclopentyl or cyclohexyl, heteroaryl is selected from optionally substituted thienyl, furyl, pyrano, pyrrolo, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, triazolyl, pyrazinyl and pyridyl and cycloheteroalkyl is selected from optionally substituted pyrrolidinyl, piperidinyl and tetrahydrofuryl  
10       and tetrahydropyran.

15       3.        The compound according to claim 1, wherein R<sup>3</sup> is selected from H, benzyl or methyl and R<sup>1</sup> and R<sup>2</sup> are each independently selected from H, halo, (C<sub>1</sub>-C<sub>6</sub>)alkyl, cyano, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>1</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl-R and -C(O)R wherein R is H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>5</sub>-C<sub>10</sub>)aryl and (C<sub>5</sub>-C<sub>9</sub>)heteroaryl; with the provisos that when R<sup>3</sup> is H then R<sup>1</sup> and R<sup>2</sup> are not both H, Br and Cl and when R<sup>3</sup> is benzyl or methyl then R<sup>1</sup> and R<sup>2</sup> are not hydrogen.

20       4.        The compound according to claim 3, wherein R<sup>1</sup> and R<sup>2</sup> are each independently selected from H, ethyl, methyl, phenyl, vinyl, fluoro, bromo, chloro, isopropyl, tert-butyl, trifluoromethyl, acetyl, propanoyl, 2,2-dimethylpropanoyl, 2-methylpropanoyl, butanoyl, pentanoyl, cyano, di-[(C<sub>1</sub>-C<sub>6</sub>)alkyl]amino, (C<sub>1</sub>-C<sub>6</sub>)monoalkylamino, (C<sub>6</sub>-C<sub>10</sub>)arylamino, (C<sub>3</sub>-C<sub>8</sub>)cycloalkylamino, heteroarylamino, cycloheteroalkyamino and CON(R<sup>5</sup>)<sub>2</sub> wherein each R<sup>5</sup> is selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl and (C<sub>6</sub>-C<sub>10</sub>)aryl; (C<sub>6</sub>-C<sub>10</sub>)aryl and (C<sub>5</sub>-C<sub>9</sub>)heteroaryl wherein the aryl and heteroaryl groups are optionally substituted with one or more substituents selected from halogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, hydroxy, hydroxymethyl, CHO and CO<sub>2</sub>R.

25       5.        The compound according to claim 4, wherein R<sup>3</sup> is selected from hydrogen, optionally substituted benzyl or (C<sub>1</sub>-C<sub>6</sub>)alkyl, wherein the substituents are described above and R<sup>1</sup> and R<sup>2</sup> are each independently selected from hydrogen, halo, cyano, optionally substituted (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkenyl, amino, di-[(C<sub>1</sub>-C<sub>6</sub>)alkyl]amino, (C<sub>1</sub>-C<sub>6</sub>)monoalkylamino, (C<sub>6</sub>-C<sub>10</sub>)arylamino, (C<sub>3</sub>-C<sub>8</sub>)cycloalkylamino, heteroarylamino, cycloheteroalkyamino and CON(R<sup>5</sup>)<sub>2</sub> wherein each R<sup>5</sup> is selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl and (C<sub>6</sub>-C<sub>10</sub>)aryl; -C(O)R wherein R is H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>5</sub>-C<sub>10</sub>)aryl and (C<sub>5</sub>-C<sub>9</sub>)heteroaryl; (C<sub>6</sub>-C<sub>10</sub>)aryl or (C<sub>5</sub>-C<sub>9</sub>)heteroaryl wherein the substituents are described above.

30       6.        The compound according to claim 5, wherein R<sup>1</sup> and R<sup>2</sup> are each independently selected from hydrogen isopropyl, tert-butyl, trifluoromethyl, acetyl, propanoyl, 2,2-dimethylpropanoyl, 2-methylpropanoyl, butanoyl, pentanoyl, cyano, 2,4-difluorophenyl, 2-fluorophenyl, 2- and 3-thienyl, dimethylamino and R<sup>3</sup> is selected from hydrogen, benzyl, methyl and R<sup>1</sup> and R<sup>2</sup> are each independently selected from hydrogen, bromo, chloro, ethyl, methyl, fluoro, vinyl and phenyl.

35       7.        The compound according to claim 1 selected from  
9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;

5                   11-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
10                   9,11-difluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-  
one;  
                  9-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9,11-diethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
15                   9-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9,11-dimethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-  
one;  
                  9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
20                   11-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9,11-diphenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-  
one;  
                  9-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
25                   9,11-divinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9-bromo-3-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-  
8-one;  
                  3-benzyl-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-  
8-one; and  
30                   3-benzyl-9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-  
8-one.  
8.                   The compound according to claim 1 selected from  
9-morpholino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-benzylamino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-  
35                   one;  
                  9-pyrrolidino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-dimethylamino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-  
one;  
                  9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

5 9-(2-tetrahydrofuryl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-ethynyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

10 9-(2-propenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-(2-propyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

15 9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-(2-methoxyphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

20 9-[2-(1,1,1-trifluoromethyl)propenyl]-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-(4-methoxyphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

25 9-(2-ethoxy-5-methylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-(2-benzofuranyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

30 9-(2-thienyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-(3-thienyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-[3-(4-methylthienyl)]-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

35 9-[2-(3-methylthienyl)]-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-[3-(2-fluoropyridyl)]-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

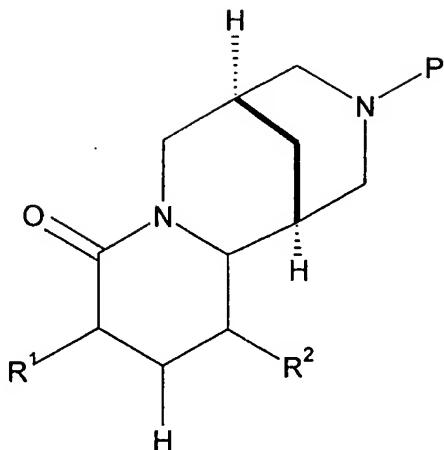
9-(2-pyridyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-(2-furanyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-(3-furanyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

5                   9-(2-trifluoromethylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a]  
[1,5]diazocin-8-one;  
                  9-(4-trifluoromethylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a]  
[1,5]diazocin-8-one;  
                  9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
10                  11-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
                  9-(2-methylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
                  9-(3-acetylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
15                  9-(2-chlorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
                  9-(3,4-dichlorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
                  9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
20                  9-(4-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
                  9-(3-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
25                  9-(3,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
                  9-(2,4-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
                  9-(2-fluoro-4-chlorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a]  
30                  [1,5]diazocin-8-one;  
                  9-(2-fluoro-4-methoxyphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a]  
[1,5]diazocin-8-one;  
                  9-(2,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one; and  
35                  9-(2-thiazoyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one.

5 9. A compound of the formula



III

wherein P is defined as R<sup>3</sup> or is selected from t-butoxycarbonyl (t-BOC), acetyl, benzoyl, trifluoroacetyl and carbobenzyloxy (CBZ) and R<sup>1</sup> and R<sup>2</sup> are each independently selected from H, halo, carboalkoxy, carboxyaldehyde, cyano, ethynyl, acyl, 2-propenyl, amino, mono and dialkylamino, boronic acid, aryl and heteroaryl with the proviso that R<sup>1</sup> and R<sup>2</sup> are not both hydrogen.

10

10. The compound according to claim 9, wherein P is t-BOC, acetyl and trifluoroacetyl and each R<sup>1</sup> and R<sup>2</sup> is independently selected from hydrogen, fluoro, bromo, chloro, iodo, (C<sub>1</sub>-C<sub>6</sub>)alkyl, carboalkoxy, carboxyaldehyde, cyano, acetyl, propanoyl, 2,2-dimethylpropanoyl, 2-methylpropanoyl, butanoyl, pentanoyl, 2-propenyl, dimethylamino, boronic acid with the proviso that R<sup>1</sup> and R<sup>2</sup> are not both hydrogen.

15

11. The compound according to claim 9, selected from

N-t-BOC-9-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

20 N-t-BOC-9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

N-cBz-9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

N-trifluoroacetyl-9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

25 N-trifluoroacetyl-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

N-trifluoroacetyl-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

N-acetyl-9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

N-tBOC-9-boronic acid -1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

N-acetyl-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

N-t-BOC-9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

N-trifluoroacetyl-9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

N-cBz-9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

N-acetyl-9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

N-t-BOC-9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

N-t-BOC-9-ethynyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

N-t-BOC-9-dimethylamino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

N-t-BOC-9-(2-propenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

N-t-BOC-9-(2-propyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

N-t-BOC-9-(2-(1,2-propanediol)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

N-t-BOC-9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

N-t-BOC-9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

N-t-BOC-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;

N-t-BOC-11-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;

N-t-BOC-9,11-dibromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one (9,11-dibromo-t-BOC-cytisine);

5            N-t-BOC-9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;

          N-t-BOC-11-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;

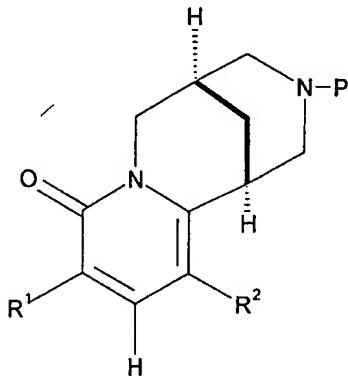
          N-t-BOC-9,11-dichloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;

10           N-t-BOC-9-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;

          N-t-BOC-11-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one; and

15           N-t-BOC-9,11-difluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one.

## 12.    A compound of the formula



## II

wherein P is selected from t-butoxycarbonyl (t-BOC), acetyl, benzoyl, trifluoroacetyl and carbobenzyloxy (CBZ) and R<sup>1</sup> and R<sup>2</sup> are each independently selected from H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkenyl and (C<sub>6</sub>-C<sub>10</sub>)aryl with the proviso that R<sup>1</sup> and R<sup>2</sup> are not both hydrogen.

13.    The compound according to claim 12 wherein R<sup>1</sup> and R<sup>2</sup> are each independently selected from H, ethyl, methyl, vinyl and phenyl.

14.    The compound according to claim 13 selected from

25           N-t-BOC-11-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one (11-vinyl-t-BOC-cytisine);

          N-t-BOC-9-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one (9-vinyl-t-BOC-cytisine);

5            N-t-BOC-9,11-divinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one  
(9,11-divinyl-t-BOC-cytisine);  
              N-t-BOC-11-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one  
(11-ethyl-t-BOC-cytisine);  
              N-t-BOC-9-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one (9-  
10        ethyl-t-BOC-cytisine);  
              N-t-BOC-9,11-diethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one  
(9,11-diethyl-t-BOC-cytisine);  
              N-t-BOC-11-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one  
(11-methyl-t-BOC-cytisine);  
15        N-t-BOC-9-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one  
(9-methyl-t-BOC-cytisine);  
              N-t-BOC-9,11-dimethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-  
one (9,11-dimethyl-t-BOC-cytisine);  
              N-t-BOC-11-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one  
20        (11-phenyl-t-BOC-cytisine);  
              N-t-BOC-9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one  
(9-phenyl-t-BOC-cytisine); and  
              N-t-BOC-9,11-diphenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-  
one (11-diphenyl-t-BOC-cytisine).  
25        15.       The compound according to claim 1 comprising racemates, stereoisomers and  
mixtures thereof.  
              16.       The compound according to claim 1 comprising at least one radiolabel selected  
from  $^3\text{H}$ ,  $^{11}\text{C}$ ,  $^{14}\text{C}$ ,  $^{18}\text{F}$ ,  $^{123}\text{I}$  and  $^{125}\text{I}$ .  
              17.       The compound according to claim 16 wherein said radiolabel is  $^3\text{H}$ .  
30        18.       The compound according to claim 16 wherein said radiolabel is  $^{11}\text{C}$ .  
              19.       The compound according to claim 16 wherein said radiolabel is  $^{14}\text{C}$ .  
              20.       A pharmaceutical composition for use in reducing nicotine addiction or to aid in  
the cessation or lessening of tobacco use in a mammal comprising an amount of a compound of  
claim 1, or a pharmaceutically acceptable salt or prodrug thereof, effective in reducing nicotine  
35        addiction, also for the prevention and treatment of withdrawal symptoms caused by cessation of  
chronic or long term use of tobacco products and a pharmaceutically acceptable carrier.  
              21.       The composition of claim 20 wherein the compound of formula I is selected from  
9-morpholino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
              9-benzylamino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

5        9-pyrrolidino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-dimethylamino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-tetrahydrofuryl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-  
one;  
10      9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-ethynyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-propenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-propyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
15      9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-methoxyphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-[2-(1,1,1-trifluoromethylpropenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a]  
20      [1,5]diazocin-8-one;  
9-(4-methoxyphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-ethoxy-5-methylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a]  
[1,5]diazocin-8-one;  
9-(2-benzofuranyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
25      9-(2-thienyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(3-thienyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-[3-(4-methylthienyl)]-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-  
one;  
9-[2-(3-methylthienyl)]-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-  
30      one;  
9-[3-(2-fluoropyridyl)]-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-pyridyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-furanyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(3-furanyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
35      9-(2-trifluoromethylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a] [1,5]diazocin-  
8-one;  
9-(4-trifluoromethylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a] [1,5]diazocin-  
8-one;  
9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

5 11-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-methylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(3-acetylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-chlorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(3,4-dichlorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-  
10 one;  
9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(4-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(3-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(3,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
15 9-(2,4-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-fluoro-4-chlorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-fluoro-4-methoxyphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
20 9-(2,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-thiazoyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
25 11-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9,11-difluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
30 11-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9,11-diethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9,11-dimethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
35 9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9,11-diphenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;

5           9,11-divinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9-bromo-3-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
3-benzyl-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
and  
3-benzyl-9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one.

10          22.     A method for reducing nicotine addiction in a mammal, comprising administering to a mammal an amount of a compound of claim 1, or a pharmaceutically acceptable salt or prodrug thereof, effective in reducing nicotine addiction and also for the treatment or prevention of withdrawal symptoms caused by cessation of chronic or long term use of tobacco products.

15          23.     The composition of claim 22 wherein the compound of formula I is selected from  
9-morpholino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-benzylamino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-  
one;  
9-pyrrolidino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-dimethylamino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-  
one;  
9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-tetrahydrofuranyl)-1,2,3,4,5,6-hexahydro-1,5-methano-  
pyrido[1,2a][1,5]diazocin-8-one;  
9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

20          25.     9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-ethynyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-propenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-  
one;  
9-(2-propyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

25          30.     9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-  
one;  
9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-  
one;  
9-(2-methoxyphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-  
pyrido[1,2a][1,5]diazocin-8-one;

30          35.     9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-  
pyrido[1,2a][1,5]diazocin-8-one;  
9-[2-(1,1,1-trifluoromethylpropenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-  
pyrido[1,2a][1,5]diazocin-8-one;

5                   9-(4-methoxyphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
10                  9-(2-ethoxy-5-methylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
15                  9-(2-benzofuranyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
20                  9-(2-thienyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
25                  9-(3-thienyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
30                  9-[3-(4-methylthienyl)]-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
35                  9-[2-(3-methylthienyl)]-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
40                  9-[3-(2-fluoropyridyl)]-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
45                  9-(2-pyridyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
50                  9-(2-furanyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
55                  9-(3-furanyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
60                  9-(2-trifluoromethylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
65                  9-(4-trifluoromethylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
70                  9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
75                  11-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
80                  9-(2-methylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
85                  9-(3-acetylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
90                  9-(2-chlorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
95                  9-(3,4-dichlorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
100                 9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
105                 9-(4-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

5	9-(3-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
	9-(3,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
10	9-(2,4-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
	9-(2-fluoro-4-chlorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
	9-(2-fluoro-4-methoxyphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
15	9-(2,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
	9-(2-thiazoyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
	9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
	11-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
20	9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
	11-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
	9-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
	11-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
	9,11-difluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-
25	one;
	9-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
	11-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
	9,11-diethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
30	9-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
	11-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
	9,11-dimethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-
	one;
	9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
	11-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
35	9,11-diphenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-
	one;
	9-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
	11-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
	9,11-divinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;

5 9-bromo-3-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-  
8-one;  
3-benzyl-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-  
8-one; and  
3-benzyl-9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-  
10 8-one.

24. The compound according to claim 1 wherein said pharmaceutically acceptable acid addition salts are the salts of acids selected from the group comprising hydrochloric acid, p-toluenesulfonic acid, fumaric acid, citric acid, succinic acid, salicyclic acid, oxalic acid, hydrobromic acid, phosphoric acid, methanesulfonic acid, tartaric acid, di-p-toloyl tartaric acid, 15 maleic and mandelic acid.

25. A method for treating addictive disorders and neurological or mental disorders related to a decrease in cholinergic function in a mammal which comprises administering to said mammal an amount of a compound of claim 1 effective in treating addictive disorders and neurological or mental disorders related to a decrease in cholinergic function.

26. The method of claim 25 wherein said addictive disorders and neurological or mental disorders related to a decrease in cholinergic function in a mammal are selected from Huntington's Chorea, tardive dyskinesia, hyperkinesia, mania, dyslexia, schizophrenia, analgesia, attention deficit disorder (ADD), multi-infarct dementia, age related cognitive decline, epilepsy, neurological and mental disorders related to a decrease in cholinergic function, senile dementia of 25 the Alzheimer's type, Parkinson's disease, attention deficit hyperactivity disorder (ADHD), anxiety, obesity, Tourette's Syndrome, ulcerative colitis,

27. The method of claim 26 wherein the compound of formula I is selected from  
9-morpholino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-benzylamino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-  
30 one;  
9-pyrrolidino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-dimethylamino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-  
one;  
9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
35 9-(2-tetrahydrofuranyl)-1,2,3,4,5,6-hexahydro-1,5-methano-  
pyrido[1,2a][1,5]diazocin-8-one;  
9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-ethynyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

5	9-(2-propenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
	9-(2-propyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
	9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
10	9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
	9-(2-methoxyphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
	9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
15	9-[2-(1,1,1-trifluoromethylpropenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
	9-(4-methoxyphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
20	9-(2-ethoxy-5-methylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
	9-(2-benzofuranyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
	9-(2-thienyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
25	9-(3-thienyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
	9-[3-(4-methylthienyl)]-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
	9-[2-(3-methylthienyl)]-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
30	9-[3-(2-fluoropyridyl)]-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
	9-(2-pyridyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
	9-(2-furanyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
	9-(3-furanyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
35	9-(2-trifluoromethylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
	9-(4-trifluoromethylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
	9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

5                    11-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-methylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
8-one;  
9-(3-acetylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
8-one;  
10                  9-(2-chlorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(3,4-dichlorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
15                  8-one;  
9-(4-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(3-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
20                  9-(3,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2,4-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-fluoro-4-chlorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
25                  [1,5]diazocin-8-one;  
9-(2-fluoro-4-methoxyphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
30                  9-(2-thiazoyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
35                  9-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9,11-difluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
one;  
9-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;

5 11-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9,11-diethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9,11-dimethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-  
10 one;  
9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9,11-diphenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-  
one;  
15 9-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9,11-divinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9-bromo-3-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-  
8-one;  
20 3-benzyl-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-  
8-one; and  
3-benzyl-9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-  
8-one.

28. A composition for treating addictive disorders and neurological or mental  
25 disorders related to a decrease in cholinergic function in a mammal comprising their  
pharmaceutically carrier and an amount of a compound of claim 1 effective in treating addictive  
disorders and neurological or mental disorders related to a decrease in cholinergic function.

29. The composition of claim 28 wherein said addictive disorders and neurological or  
mental disorders related to a decrease in cholinergic function in a mammal are selected from  
30 Huntington's Chorea, tardive dyskinesia, hyperkinesia, mania, dyslexia, schizophrenia, analgesia,  
attention deficit disorder (ADD), multi-infarct dementia, age related cognitive decline, epilepsy,  
neurological and mental disorders related to a decrease in cholinergic function, senile dementia of  
the Alzheimer's type, Parkinson's disease, attention deficit hyperactivity disorder (ADHD), anxiety,  
obesity, Tourette's Syndrome and ulcerative colitis.

35 30. The composition of claim 28 wherein the compound of formula I is selected from  
9-morpholino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-benzylamino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-  
one;  
9-pyrrolidino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

5	9-dimethylamino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one; 9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one; 9-(2-tetrahydrofuryl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
10	9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one; 9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one; 9-ethynyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one; 9-(2-propenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
15	9-(2-propyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one; 9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one; 9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
20	9-(2-methoxyphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one; 9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
25	9-[2-(1,1,1-trifluoromethylpropenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one; 9-(4-methoxyphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one; 9-(2-ethoxy-5-methylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
30	9-(2-benzofuryl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one; 9-(2-thienyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one; 9-(3-thienyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
35	9-[3-(4-methylthienyl)]-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one; 9-[2-(3-methylthienyl)]-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one; 9-[3-(2-fluoropyridyl)]-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

5                    9-(2-pyridyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-furanyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(3-furanyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-trifluoromethylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a]  
[1,5]diazocin-8-one;  
10                  9-(4-trifluoromethylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a]  
[1,5]diazocin-8-one;  
                      9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
11-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-methylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-  
15                8-one;  
                      9-(3-acetylphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-  
8-one;  
                      9-(2-chlorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-  
8-one;  
20                9-(3,4-dichlorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-  
pyrido[1,2a][1,5]diazocin-8-one;  
                      9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-  
8-one;  
                      9-(4-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-  
25                8-one;  
                      9-(3-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-  
8-one;  
                      9-(3,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-  
pyrido[1,2a][1,5]diazocin-8-one;  
30                9-(2,4-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-  
pyrido[1,2a][1,5]diazocin-8-one;  
                      9-(2-fluoro-4-chlorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a]  
[1,5]diazocin-8-one;  
                      9-(2-fluoro-4-methoxyphenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a]  
35                [1,5]diazocin-8-one;  
                      9-(2,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-  
pyrido[1,2a][1,5]diazocin-8-one;  
                      9-(2-thiazoyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
                      9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;

5                   11-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
10                   9,11-difluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-  
one;  
                  9-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9,11-diethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
15                   9-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9,11-dimethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-  
one;  
                  9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
20                   11-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9,11-diphenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-  
one;  
                  9-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
11-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
25                   9,11-divinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9-bromo-3-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-  
8-one;  
                  3-benzyl-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-  
8-one; and  
30                   3-benzyl-9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-  
8-one.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/IB 97/01282

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 C07D471/18 A61K31/44 A61K31/455 A61K31/455  
//(C07D471/18,221:00,221:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PARTHEIL A.: "52. Über Cytisin und Ulexin. II. Abhandlung" ARCHIV DER PHARMAZIE (WEINHEIM), vol. 232, 1894, pages 161-177, XP002050586 see page 173 ---	9,10
X	LAMMERS J.: "77. Beiträge zur Kenntnis des Cytisins" ARCHIV DER PHARMAZIE (WEINHEIM), vol. 235, 1897, pages 374-397, XP002050587 see page 392 --- -/-	1

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&\* document member of the same patent family

2

Date of the actual completion of the international search

18 December 1997

Date of mailing of the international search report

23.01.98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl  
Fax: (+31-70) 340-3016

Authorized officer

Hartrampf, G

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 97/01282

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ISKANDEROV S. ET AL.: "Dimethamine - a new bimolecular alkaloid" CHEMISTRY OF NATURAL COMPOUNDS (ENGL. TRANSL.), vol. 8, 1972, page 216 XP002050588 see structure II see page 217 ---	1
X	EP 0 581 457 A (R.J. REYNOLDS TOBACCO COMPANY) 2 February 1994 see the whole document ---	1,3-6,9, 28,29
X	WINK M. ET AL.: "Patterns of quinolizidine alkaloids in 56 species of the genus lupinus" PHYTOCHEMISTRY, vol. 38, no. 1, January 1995, pages 139-153, XP002050589 see page 140; 7th compound ---	1,3,9,15
Y	CHEMICAL ABSTRACTS, vol. 99, no. 26, 26 December 1983 Columbus, Ohio, US; abstract no. 218594n, TALAPIN V.I. ET AL.: "Pharmaceuticals as smoking deterrents" page 385; column 1; XP002050590 see abstract & WO 83 02892 A (BELORUSSIAN SCIENTIFIC-RESEARCH INSTITUTE OF SANITATION AND HYGIENE) 1 September 1983 ---	1,20,28
Y	US 4 835 162 A (ABOOD L.G.) 30 May 1989 see table 3 ---	1,20,28
Y	WO 95 11678 A (DYNAGEN INC.) 4 May 1995 see page 7; claims 1,12,20 -----	1,20,28

**INTERNATIONAL SEARCH REPORT**

International application No.  
PCT/IB 97/01282

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: **22,25-27**  
because they relate to subject matter not required to be searched by this Authority, namely:  
**Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy**
  
2.  Claims Nos.: **9**  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
**The formula (III) in claim 9 is defined differently to that in the description page 8**
  
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

Int. Appl. No.

PCT/IB 97/01282

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 581457 A	02-02-94	US 5242916 A		07-09-93
		JP 6122629 A		06-05-94
US 4835162 A	30-05-89	US 4966916 A		30-10-90
WO 9511678 A	04-05-95	US 5414005 A		09-05-95
		AU 1045695 A		22-05-95
		AU 8096094 A		22-05-95
		CA 2174747 A		04-05-95
		EP 0725640 A		14-08-96
		JP 9507053 T		15-07-97
		WO 9511679 A		04-05-95